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FBG, fasting blood glucose; HbA1c, (glycated) haemoglobin A1c; PPBG, post-prandial blood glucose; T2DM, type 2 diabetes mellitus

References: **1.** SEMAGARD Professional Information, July 2026. **2.** Sun Pharmaceutical Industries Ltd. Data on file: GLP-1 pricing. June 2026.

3a. Sun Pharmaceutical Industries Ltd. Data on file: Semagard bioequivalence study [SEM01024]. **3b.** Gopalakrishnan UA, Joshi AS, Giri R, et al. Semaglutide injection in Indian patients with type 2 diabetes mellitus: a randomised, phase III active-controlled study. *Diabetes Obes Metab.* 2026;0:1-10. doi:10.1111/dom.70891. **4.** Sun Pharmaceutical Industries Ltd. Data on file: Semaglutide professional information. February 2023. **5.** About us. Sun Pharma. Accessed June 10, 2026. <https://sunpharma.com/about-us/>

[S4] SEMAGARD (Solution for Injection). Reg. No.: 61/21.13/0768. Each 1 ml solution contains 1,34 mg of semaglutide. Preservative: phenol 5,50 mg/ml (0,55 % m/v). Contains propylene glycol 14 mg/ml. SEMAGARD 0,25 mg and 0,5 mg/dose pen: Each pre-filled pen contains 2 mg semaglutide in 1,5 ml solution. SEMAGARD 1 mg/dose pen: Each pre-filled pen contains 4 mg semaglutide in 3 ml solution. For full prescribing information, refer to the Professional Information approved by the Regulatory Authority.

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UTROGESTAN	851957-005	S4	Micronised progesterone	100 mg	Capsules	30

Reference: 1. Lokkegaard E et al. Eur Heart J 2008;29:2660-8. 2. Renoux C et al. BMJ 2012;340:c2519. 3. de Lauzon-Guillain, Fournier A, et al. Diabetologia 2009;52:2092-100. 4. L'Hermite M et al. Maturitas 60;2008:185-201. 5. Mueck A.O. CLIMACTERIC 2012;15(Suppl 1):11-7. 6. P. Stute et al. Climacteric 2018, 21:2, 111-122.

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

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

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.

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It has been almost a year since the announcement that the South African Pharmaceutical Journal (SAPJ) had been granted official accreditation, and this took place during the first full year of the Department of Higher Education & Training (DHET) receiving its accreditation (July 2025 to July 2026). Compared with the year before DHET accreditation (July 2024 to July 2025), the first accreditation year (July 2025 to July 2026) saw a clear rise in activity: submissions increased from 157 to 199 (about 27%), acceptances from 109 to 128 (around 17%), and publications from 102 to 123 (just over 20%).

The DHET accreditation gives the SAPJ an academic stamp; how this translates into practice requires consideration of the question 'What kind of **impact** matters most for South African pharmacists? Does the publishing of educational knowledge and perceptions studies in any way change undergraduate and postgraduate teaching or CPD activities? Similarly, do the product-focused pieces support rational, evidence-based use rather than marketing hype?

The SAPJ is unique in that it is both an accredited research journal and a practice journal. Our pages are multi-voiced, and include original research, review articles, pharmacy practice pieces, product focus content, letters, obituaries and short reflections such as 'Nibbles'. During this period we introduced CPD questions as a regular feature in SAPJ. In parallel, we have strengthened the peer-review process for research and other scholarly submissions. Having an accredited, multi-voiced journal gives us a unique opportunity for transdisciplinary knowledge transfer across practice, academia and industry.

The peer-review process involves a few clear steps. Every research manuscript that passes initial editorial screening is sent to the relevant section editor, who in turn selects at least two independent reviewers chosen for their subject expertise. These reviewers are asked to comment on the scientific quality, practical relevance, ethical soundness (amongst other factors) and clarity of each submission, and authors are expected to respond to these comments in a transparent revision process. This process is built for purpose: to ensure that the published work maintains academic integrity and is usable in practice.

When I look at the publication numbers, what strikes me most is how many people already trust the SAPJ with their work. Over the past three years we have handled more than 400 submissions and published over 270 papers ranging from original research and reviews to CPD, practice pieces, product-focused articles and letters. That volume is only possible because colleagues have been willing to contribute as reviewers and authors were willing to submit research papers to a then unaccredited journal. Thank you.

When I approach fellow pharmacists for these opportunities, many still tell me, almost apologetically, "I'm not really a researcher". I don't

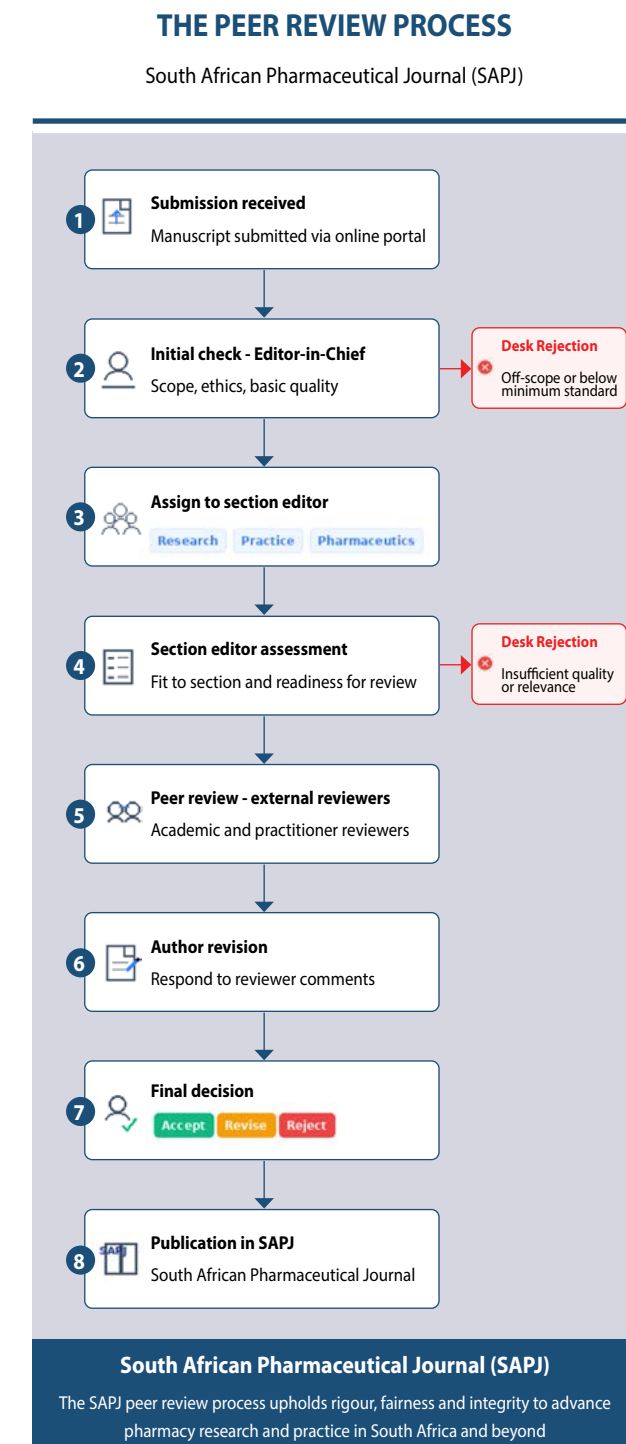


Figure 1

believe that. If you have completed a pharmacy degree/diploma, you already read, weigh up and apply evidence every day, you are a scientist by training, even if your job title does not say "researcher".

Some of the most important papers we can publish in SAPJ will not come from large projects with statisticians and grant numbers attached. They will come from medication review/other audits (economically and other) in a busy dispensary, a well-described case report, a service that was redesigned to solve a local problem (using Ai or other workflows), or a teaching practice innovation that worked. If you can keep notes, reflect on what you did, and why it mattered, you can write.

Now, more than ever, we need even more of our colleagues to join the process. I would especially like to invite community, hospital and industrial pharmacists to register as reviewers, and to send us practiceoriented case reports and letters to the editor that speak honestly about realworld dilemmas, any innovations and lessons learned. These contributions will be what **keeps** the SAPJ accredited

(with better 'numbers'), and reflect **a true record** of South African pharmacy practice. If you would like to be a reviewer, please email your name, email address and areas of expertise to Robyn Marais at robyn@jesser-point.co.za so that she can include you on our reviewers' list.

So where should you send your work if you want it to make a difference to pharmacy practice in South Africa and other countries? I would argue that the SAPJ is one of those places. We will continue to refine how we think about impact, tracking not only citations but also downloads, page views, CPD usage, teaching uptake and references in policy and guidelines. And if something you read here resonates with you, please write back to us in a letter, a case report, a practice paper or a proposal to review. That, too, is a form of impact.

Letter to the editor



On Monday, 22 June 2026, a staff member of the PSSA National Office attended a Private Sector Consultation on Adolescent Pregnancy, organised by the Department of Women, Youth & Persons with Disabilities in the Presidency, in collaboration with the United Nations Population Fund (UNFPA), Bayer, and Organon.

During the programme, Dr Ntlotleng Mabena read a poem she wrote, and although it focuses on adolescent pregnancy, it is hard-hitting for pharmacists and pharmacy support personnel, irrespective of your area of practice. Pharmacy has become a numbers game – how many batches you manufactured and released, how many orders were packed and shipped, how many scripts you did today, how many sales you made...

Pharmacists have long been among the most trusted professionals worldwide, and one reason we have been able to earn this trust is our ability to see the patient behind the prescription or the number. So, in this current environment, try to remember the person behind the number or your screen and know that seeing the patient can change their world. Just like dropping a small stone in the water causes larger and larger ripples, each change you can create in someone's life will have a ripple effect on their family, their community and even the economy in the end. A healthy, growing economy needs a healthy population, and YOU as an individual can make a difference.

Dr Ntlotleng Mabena is a public health clinician, an academic, and a social justice and social medicine activist. In addition to a medical degree, Ntlotleng also has a Master's in Public Health, a Diploma in HIV Management, a Diploma in Tropical Medicine and Hygiene, a Post Graduate Diploma in Clinical Forensic Medicine, and a Graduate Certificate in Lesbian, Gay, Bisexual, and Transgender Health Policy and Practice from George Washington University, USA. Ntlotleng was born and raised in Mamelodi, a township in Tshwane, South Africa. Her passion lies in working with marginalised women and helping to ensure that all women, especially those at the margins of society, have access to quality primary healthcare services. Ntlotleng currently works with the Networking HIV & AIDS Community of Southern Africa as the Gender-Based Violence Technical Specialist, ensuring that the health system, including healthcare workers, is appropriately trained and equipped to provide services to survivors with dignity and compassion. She also runs her own organisation, Open House Initiative, where they provide psychosocial support to young queer females and assist them in leading productive lives. Ntlotleng describes themselves as an intersectionalist, working to transform people from where they are currently and to spark the desire to identify this true purpose and follow that dream.

Before you talk numbers...

By: Dr Ntlotleng Mabena

Before you talk numbers,
remember:
that "case" on your slide is me.

Not a percentage.

A person.

Teenage pregnancy.

You say it like a headline.

While I feel it like:

shame, guilt, embarrassment, trauma,
me judging myself,
others judging me,
disappointment so loud
I stop trusting my own feelings.

You talk about "falling pregnant"
as though pregnancy is a ditch
a girl stumbles into in the dark.
But who turned off the lights?

If you really want to help,
don't start with my womb,
start with my world.

Make it easy for me

to ask questions,

to get condoms, pills, information,
without side eyes and lectures.

Make help simple, kind,
and there when I actually need it—
not only from 8 to 4.

If what you decide today
can remove even one of those barriers,
then maybe one girl, one boy,
walks a different path tonight.

Then you can say

you didn't just talk about us—
you showed up for us.

Before you talk numbers,
look at me,
and remember

I am not your problem to fix.
I am your partner

Because when I rise,
those numbers shift.

When I am supported,
those outcomes change.

When I am seen,
those statistics become stories of possibilities
not just survival.

For all of us.

Truth.

Where foreign particles can become a problem

Safety factor – Industrial vacuums in the pharmaceutical industry

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KÄRCHER

In pharmaceutical manufacturing, cleanliness is not just a quality requirement; it is a regulatory obligation. Production environments must comply with strict Good Manufacturing Practice (GMP) standards to ensure patient safety, product efficacy and brand integrity. While many facilities integrate automated extraction and dust control systems into their processes, manual cleaning with industrial vacuums remains essential. Foreign particles, active pharmaceutical ingredients (APIs), excipients or packaging residues can compromise product quality and lead to costly batch rejections or recalls. For manufacturers and cleaning service providers alike, maintaining validated cleaning procedures is critical to preventing contamination and protecting company reputation.



Foreign particles in pharmaceutical production: Where to look (1)

Pharmaceutical plants contain a variety of controlled environments, from granulation and tableting areas to capsule filling, coating and packaging lines. Each zone has specific containment requirements. Fine powders generated during blending or compression are often highly potent and may pose inhalation risks. In certain concentrations, airborne dust can also present an explosion hazard, particularly when handling organic compounds.

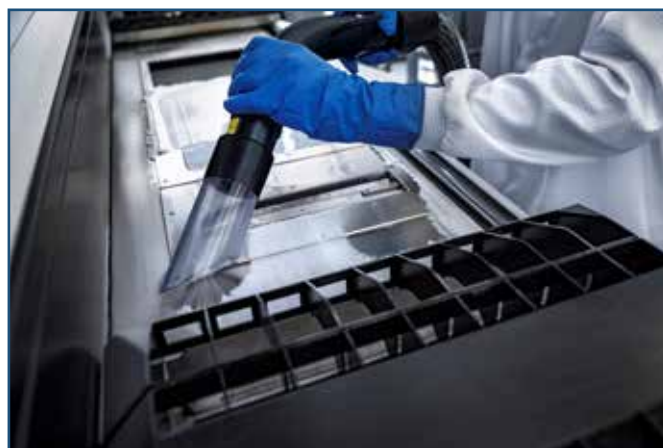
Beyond operator safety, cross-contamination is one of the greatest risks. Residual powder settling on equipment frames, cable trays, air ducts or floors can migrate into subsequent batches. Even microscopic traces of a previous product may result in out-of-specification results. In sterile or high-care areas, the presence of foreign particles can lead to immediate batch rejection.

Regular manual cleaning with compliant industrial vacuums is therefore required alongside built-in extraction systems. Production machinery, change parts, transfer lines, walls and especially floors must be thoroughly cleaned. Floors deserve particular attention, not only for hygiene reasons but also to prevent slip hazards caused by spilled powders or liquids.

Foreign particles in pharmaceutical changeovers: Where to look (2)

During product changeovers, validated cleaning is mandatory to prevent cross-contamination between different formulations, strengths or therapeutic categories. In some cases, cleaning can take longer than the production run itself. Industrial vacuums support efficient removal of residual powders before wet cleaning or disinfection begins, reducing overall downtime while maintaining compliance.

In the event of spills involving APIs, solvents or intermediates, immediate containment is vital. The safe recovery of hazardous substances protects both personnel and the cleanroom



environment. In high-containment facilities, vacuum systems may also be integrated into isolators or used as mobile units designed for controlled dust-free disposal.

What to look out for:

The basics of industrial vacuums

Pharmaceutical production environments demand robust, hygienic and easy-to-sanitise equipment. Stainless steel construction with smooth, crevice-free surfaces is preferred to prevent particle accumulation and support effective cleaning validation. Painted components are unsuitable, as flaking coatings may introduce contamination risks.

Performance must match the application. Larger hose diameters are suitable for higher volumes of powder, while compact systems

with smaller hoses are ideal for confined cleanroom spaces. For continuous or multi-shift use, three-phase machines are generally recommended over standard AC units due to their durability and runtime capacity.

Filtration is equally critical. Depending on the hazard level of the material, vacuums must comply with dust classes L, M or H. Highly potent or toxic substances typically require dust class H filtration, ensuring safe retention and disposal. Where combustible dust is present, compliance with ATEX guidelines is essential to prevent ignition in classified zones.

Integrating industrial vacuums into validated cleaning processes reduces risk, improves efficiency and safeguards product integrity. In the pharmaceutical industry, effective particle control is not an optional extra – it is a fundamental component of operational success.



President's Message

Staying relevant in a changing healthcare environment

There is something fascinating about both penguins and pangolins.

African penguins are highly social animals. They communicate through distinct vocal sounds, work together in groups, and are incredibly resilient in harsh coastal environments. Pangolins, on the other hand, are quiet, careful, and highly specialised creatures. Their scales protect them, and they play an important role in maintaining balance in ecosystems by controlling insect populations.

Yet despite these remarkable qualities, both species are on the endangered list. Their stories remind us of an important lesson: even species with unique strengths can become vulnerable when environments change, when pressures increase, and when their value is overlooked.

As pharmacists, we can learn something from this.

The healthcare environment around us is changing rapidly. Systems are under pressure. Patient expectations are evolving. Technology is reshaping healthcare delivery. Medicine access, affordability, and sustainability remain ongoing concerns. At times, the profession may feel stretched, uncertain, or even undervalued.

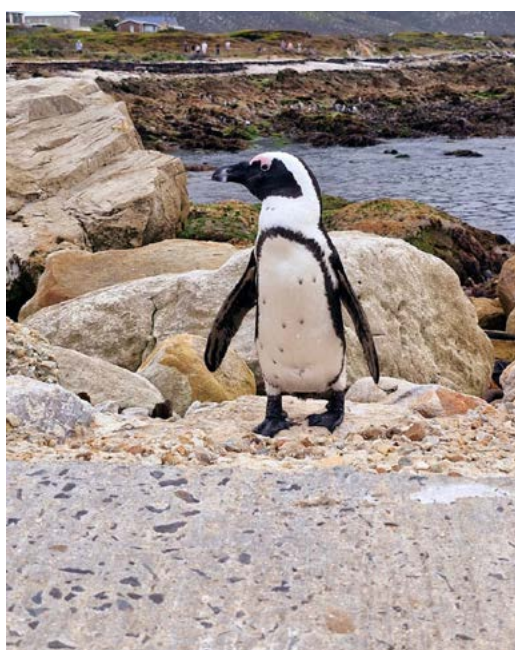
However, unlike endangered species, pharmacy is not disappearing. In fact, the profession continues to evolve and strengthen its relevance within healthcare. Pharmacists remain some of the most

accessible healthcare professionals in South Africa. Every day, pharmacists support patients, guide safe medicine use, strengthen medicine supply systems, contribute to public health programmes, and improve healthcare outcomes across communities.

The role of the pharmacist today extends far beyond dispensing medicines. Pharmacists are involved in antimicrobial stewardship, vaccination services, pharmacovigilance, chronic disease management, digital health initiatives, regulatory work, research, academia, and healthcare policy development. Across community, hospital, industrial, academic, and public sector settings, pharmacists continue to demonstrate adaptability and resilience.

This adaptability is one of the profession's greatest strengths. Healthcare will continue to evolve, and so must pharmacy. The profession cannot afford to remain passive while systems around us transform. Instead, pharmacists must continue to position themselves as essential partners in patient-centred care and healthcare delivery.

The ongoing discussions around the National Health Insurance (NHI) and the recent Constitutional Court case have once again highlighted the importance of professional engagement in healthcare reform. Whether one supports or critiques aspects of NHI implementation, one thing is clear: pharmacists cannot stand on the sidelines of these discussions.



African penguins: Betty's Bay and Boulders Beach

This moment presents an opportunity for the profession to demonstrate its value within a changing healthcare system actively. Pharmacists have expertise that South Africa cannot afford to overlook, particularly in medicine management, medicine access, patient safety, antimicrobial resistance, and primary healthcare support.

As healthcare reforms continue, the profession must ensure that pharmacy remains visible, recognised, and involved in policy and implementation discussions. Relevance does not happen automatically. It requires advocacy, leadership, collaboration, and participation.

The Pharmaceutical Society of South Africa (PSSA) continues to play an important role in ensuring that the voice of pharmacy is heard within these national conversations. As a profession, we must continue to engage constructively, contribute meaningfully, and prepare ourselves for the future healthcare environment. Please contact the national office to participate in these conversations.

The future of pharmacy may not look exactly like the present, but the need for pharmacists is not disappearing. In increasingly complex healthcare systems, the world needs medicine experts more than

ever before. Patients need professionals who can support the safe and responsible use of medicines. Health systems need individuals who understand stewardship, supply chain management, rational medicine use, and public health priorities.

And perhaps this brings us back to the penguin and the pangolin. Penguins are known for their strong sense of community and their ability to adapt to difficult environments. Pangolins are known for their protective resilience and specialised role within nature.

Interestingly, these are also qualities we see in pharmacists. Pharmacists work within communities. Pharmacists adapt. Pharmacists protect patients through safe medicine practices. Pharmacists fulfil specialised roles that are critical to healthcare systems.

The difference is this: while penguins and pangolins face the threat of extinction, pharmacists will continue to evolve and strengthen their place within healthcare. And as long as the profession continues to lead, collaborate, advocate, and innovate, pharmacy will remain relevant, visible, and essential, without worrying about being placed on any endangered list.

Renier Coetzee
PSSA President



PSSA 80 anniversary dialogue

Beyond the PSSA's festive 80th-anniversary celebrations, the Society convened a reflective dialogue on the future of pharmacy and the Society in South Africa, facilitated by Ms Elsabe Klinck, a well-known legal and regulatory voice in the health sector. The discussion focused on the profession's strengths, the implications of healthcare reform and National Health Insurance (NHI), workforce and regulatory challenges, prescribing rights, technological disruption, and the role of professional unity and leadership in shaping the future. It brought together a wide range of voices from PSSA NEC members and affirmed both the strength of pharmacy and the urgency of coordinated action to secure its future role in healthcare delivery and policy.

Pharmacy in South Africa is entering a period of significant transition. Changes in health policy, ongoing debates around the NHI, increasing pressure on public-sector resources, and rapid developments in digital technology are reshaping the professional landscape. In this context, pharmacy professionals and leaders are being compelled to reconsider the profession's technical functions alongside its broader identity, influence, and strategic direction. The dialogue revealed a profession aware of both its strengths and vulnerabilities, and a growing recognition that pharmacy can no longer afford to be reactive. Rather, it must define its own role in the evolving healthcare system, actively shape legislative, regulatory, and institutional outcomes, and consider strategies to ensure that pharmacists remain influential contributors to healthcare delivery and policy development.

A central theme in the discussion was that pharmacy has a set of strengths that distinguish it from many other healthcare professions. Participants highlighted the Society's ability to maintain a relatively unified voice despite representing diverse sectors, including community and hospital pharmacy, academia, industry, and regulatory bodies. This cohesion was presented as a major asset at a time when fragmentation often weakens other professions' ability to influence policy. Diversity was also highlighted as a defining advantage. The Society's leadership and membership increasingly reflect South Africa's demographic diversity, encompassing different racial, gender, geographic, and professional backgrounds. This diversity broadens the profession's legitimacy, responsiveness, and representativeness in meeting the healthcare needs of the population it serves.

The strength of branch structures in sustaining the profession's presence and influence was emphasised, as they enable more direct engagement with members and local stakeholders while

supporting a unified professional voice. In addition, the Society's members have extensive experience in business, organisational, and systems management. Across community, hospital, industry, regulatory, and academic settings, pharmacists routinely manage complex operational processes, including procurement, supply chain management, regulatory compliance, quality assurance, workforce coordination, financial oversight, and occupational health and safety. These responsibilities often bring a level of operational and administrative competence that extends well beyond clinical work.

In addition, pharmacy has a long-standing reputation for multidisciplinary collaboration and the early adoption of technology. The widespread use of digital systems and computerised processes across practice settings reflects the profession's ability to innovate, adapt, and respond effectively to the evolving needs of healthcare systems and patients. Pharmacy was also seen as benefiting from a relatively responsive regulator, with the South African Pharmacy Council viewed as more reform-minded than other professional councils.

Much of the discussion focused on the implications of National Health Insurance (NHI) and the uncertainty surrounding the final implementation pathway of the NHI Act, given the ongoing legal and constitutional challenges. Remarks addressed several possible outcomes of these challenges, including the possibility that public participation challenges may succeed, that broader constitutional challenges may alter implementation, that the Act may proceed substantially intact, or that litigation may result in partial amendments. Despite the different scenarios considered, there was strong agreement on one point: regardless of the specific legal outcome, major healthcare reform is inevitable, and pharmacists must prepare accordingly and actively shape their future rather than simply react to policy developments.

The key strategic question raised was not simply how pharmacy should respond to NHI, but what kind of health system the profession itself wishes to help build. Questions about reimbursement mechanisms, prescribing authorisation, medicines procurement and supply systems, workforce planning, and relationships between national and provincial health structures were identified as areas requiring clear professional consensus. It was repeatedly stressed that the profession has a limited window in which to formulate these positions in language suitable for policymakers and Parliament. The implication was that the pharmacy profession cannot rely on others to design its future

place in the health system; it must enter the reform process with precise, coherent, and actionable proposals.

Despite the uncertainty surrounding reform, several important opportunities for the profession could enhance its contribution to healthcare delivery. One opportunity relates to the growing interest in affordable healthcare funding models beyond the traditional medical scheme environment. In this context, the profession was seen as well-positioned to do so through community-based interventions and preventative care initiatives, given that community pharmacies already serve as highly accessible points of care.

Procurement reform was also highlighted as an area where pharmacists can play a greater role. Given their expertise in medicines management, participants argued that pharmacists should be actively involved in technical evaluations, procurement decision-making, and the development of transparent systems that prioritise clinical appropriateness and patient outcomes. Without such involvement, there is a risk that medicine procurement could be driven primarily by administrative or financial considerations rather than by therapeutic appropriateness and public health need.

Price regulation was also identified as an important policy frontier. As the government considers new pricing frameworks to regulate healthcare providers, there is an emphasis on the need for the profession to engage proactively to ensure that pharmacists are appropriately represented and that the unique nature of pharmaceutical services is recognised; otherwise, they could be inappropriately grouped with other provider categories. Closely related to this was the issue of human resources and workforce planning. Concerns were raised about frozen public-sector posts, high vacancy rates, and an increasing number of graduates entering a labour market with limited employment opportunities. These trends were seen as requiring coordinated workforce planning to align educational capacity with healthcare needs and to ensure sustainable career pathways for future pharmacists.

A particularly significant opportunity discussed was the expansion of pharmacists' prescribing rights. Participants noted that while other health professionals are increasingly gaining prescribing authority, pharmacists remain restricted despite extensive training in pharmacology and therapeutics. However, relevant legislative work is already under consideration, which would require broader recognition of pharmacists as prescribing professionals. The incorporation of prescribing competencies into undergraduate education and the expansion of clinical training opportunities were identified as important enablers of this vision.

Alongside these opportunities, several serious threats facing the profession were identified. One of the most immediate concerns was the growing bureaucracy, intensified regulatory oversight, and market scrutiny, which were described as risks that may draw pharmacists away from patient care and professional development. The widening gap between corporate and independent community pharmacies, and the effects of softer

regulation in an environment where multinational corporations may increasingly influence medicine markets and retail systems, were also noted. Commercial compounding and other questionable practices were cited as areas where professional standards may be undermined by market pressures. Technological disruption, including artificial intelligence (AI) and automation, was also seen as both an opportunity and a threat. Participants acknowledged that technology is transforming healthcare documentation, workflows, and decision-making, and warned that the profession must adapt quickly to avoid being overtaken by developments already reshaping other sectors.

The discussion on technology and AI was particularly forward-looking. Participants noted that pharmacists who effectively leverage technological tools may be better placed to deliver efficient, patient-centred care in the future, as professional competence will increasingly depend on technological fluency. At the same time, there was a clear insistence that technology should support rather than replace pharmacists. AI is viewed as a tool that can strengthen practice, improve efficiency, and enhance system-level responsiveness, but only if pharmacists remain central to its design and use. Integrating AI, data analytics, and digital health competencies into pharmacy education and professional development programmes was highlighted as crucial. The implication was that future professional relevance will depend on maintaining a balance between clinical expertise and the ability to integrate technological tools into safe, effective, and patient-centred practice.

A key outcome of the discussion was the need for the PSSA to strengthen its engagement with political, legislative, and regulatory processes. The Society was encouraged to build long-term relationships with parliamentary portfolio committees, policymakers, provincial health structures, and regulatory bodies, positioning itself as a credible, solutions-oriented partner in healthcare reform. Rather than responding only after policies are proposed, the Society should contribute proactively to policy design and implementation. This includes developing evidence-based recommendations for legislative and regulatory amendments. By translating professional expertise into practical, implementable policy solutions, the Society can increase its influence and ensure that pharmacy's perspectives are reflected in future healthcare legislation and reform initiatives.

The anniversary reflections extended beyond policy and practice to consider the profession's future identity. Participants repeatedly emphasised the need for greater visibility of pharmacists within healthcare systems, public discourse, and policy-making environments. Many expressed the view that pharmacists should be represented in all discussions affecting medicines and healthcare delivery. This concern about visibility was presented as integral to professional influence and public understanding. Public visibility, media engagement, and recognition of pharmacists as healthcare experts were therefore seen as essential strategic priorities.

A particularly important aspect of the discussion focused on

leadership development and the need for unity. Participants emphasised the need to involve younger pharmacists in leadership roles while ensuring they receive mentorship and support from experienced professionals. Leadership development was seen not as a future priority but as an immediate responsibility, requiring deliberate investment at branch and national levels through inclusion and participation in committees, governance and professional activities, as well as in environments that encourage innovation and diverse perspectives. In this regard, the Society was described as the central voice of pharmacy, a unifying structure, and a respected professional body with the institutional history to carry the profession forward. The phrase “*common problem, common solution*” captured the prevailing sentiment and the Society’s diversity was regarded as one of the profession’s greatest assets, provided it is organised around common goals and a shared vision.

The PSSA’s 80th-anniversary dialogue provided an opportunity to reflect on the pharmacy profession’s history and resilience. Elder pharmacists recalled past threats to ownership rights and professional autonomy, as well as challenging healthcare policies, and drew parallels with current challenges, including NHI and corporatisation. This historical perspective fostered optimism about the future. Participants noted that the profession has

successfully navigated significant transitions before and has the expertise, organisational structures, and leadership to address current challenges. These reflections served as a reminder that pharmacy has consistently adapted to evolving circumstances while maintaining its commitment to patient care.

The discussions also underscored the importance of social responsibility and professional stewardship. Participants emphasised the need for pharmacy organisations to continue investing in initiatives that benefit both members and the broader communities they serve. This framing of social responsibility reinforces the idea that pharmacy’s legitimacy depends not only on defending its own interests but also on demonstrating public value.

As South Africa’s healthcare landscape continues to evolve, pharmacists have an opportunity to participate in and help shape change. The profession must define its place in the future health system, engage strategically with policy and legislation, cultivate visible and credible leadership, and ensure that younger professionals are prepared to sustain and extend the profession’s influence. The reflections shared during the PSSA’s 80th-anniversary celebrations suggest that the profession is both willing and capable of meeting that challenge.

PSSA/INSIGHT continuing education programme

Module 3: Attention-Deficit Hyperactivity Disorder

Attention-deficit/hyperactivity disorder (ADHD) is a neuro-developmental disorder that presents in childhood with symptoms of hyperactivity, impulsivity and/or inattention. The notion that ADHD is a disorder of childhood prevailed until the turn of the century, but researchers have now documented the persistence of symptoms into adulthood in 60 to 70 % of patients.

ADHD is a costly, chronic disorder with a significant impact on the quality of life for patients and their families. The consequences of untreated ADHD in children can range from poor self-esteem and academic difficulties to clinically relevant mental health disorders. At the same time, problems with planning, task initiation, task

completion, impatience and impulsivity can cause numerous work-related and interpersonal problems in adults.

In February 2025, the South African Society of Psychiatrists (SASOP) and the Psychiatry Management Group (PsychMG) released updated guidelines for managing attention deficit/hyperactivity disorder in children and adolescents. These guidelines were preceded by the SASOP/PsychMG guidelines for adult ADHD, which were published in 2017.

This module discusses ADHD in children and in adults and focuses on the guideline-recommended pharmacological treatment options for the disorder in children, adolescents and adults.

PSSA/Insight pharmacy staff clinical education programme

Module 3: Attention-Deficit Hyperactivity Disorder (ADHD)

ADHD is one of the most common psychiatric disorders of childhood and adolescence and often persists into adulthood. It is a chronic disorder with a substantial impact on quality of life for patients and their families.

When left untreated, ADHD can lead to a range of difficulties—from low self-esteem, academic underperformance, and mental health challenges in children, to problems with task initiation, task completion, impulsivity, and impatience in adults, often resulting in workplace and interpersonal conflict.

This module explores ADHD in children, adolescents, and adults, equipping you as a front shop team member with a better understanding of this commonly overlooked condition. It

provides a solid knowledge base to help you confidently engage with parents and caregivers and offer informed support.

If you would like to participate in the 2026 PSSA/Insight CE programme, contact Glynis at Insight Medicine Information on 011 706 6939 or email: cpd@insightmed.co.za.

Registration and payment for the 2026 PSSA/INSIGHT CE programme is now fully online

Simply visit www.insightcpd.co.za and under Registration select:

- Previously enrolled participants – for those renewing for 2026 OR
- New participants – for those enrolling in the Programme for the first time



Youth day 50 years later: What the new age of youth leadership means for young pharmacists

Thinavhuyo Musekene

June is Youth Month in South Africa: a time for reflection, remembrance, and renewed commitment to the future. This year carries particular significance as we mark 50 years since the youth of 1976 courageously took to the streets to demand a better future. Their actions changed the course of South African history and demonstrated the power of young people to drive meaningful change.

Today, the challenges facing young South Africans may look different, but the spirit of youth leadership, resilience, and collective action remains just as important. As members of the PSSA Young Pharmacists' Group (YPG), Youth Day offers an opportunity to reflect on what it means to be a young healthcare professional in a rapidly changing world and how we can continue building a profession that serves both pharmacists and the communities we care for.

The youth of 1976 understood a powerful truth: progress is rarely achieved in isolation. Their movement was built on unity, shared purpose, and the belief that together they could overcome barriers that seemed impossible to challenge. Fifty years later, this lesson remains relevant to young pharmacists navigating the opportunities and complexities of the modern healthcare field.

Today's pharmacists are entering a profession that is constantly evolving. Advances in technology, changing patient needs, healthcare reforms, and expanding professional roles require us to adapt continuously. At the same time, many young pharmacists face challenges such as employment uncertainty, professional transitions, workload pressures, and the need to establish themselves in increasingly competitive environments.

In these circumstances, the value of community cannot be overstated. One of the defining characteristics of the YPG is its commitment to creating a network of support for young pharmacists across South Africa. Whether through mentorship, professional development initiatives, networking opportunities, podcasts, conferences, or peer engagement, the YPG provides a space where young professionals can learn from one another and grow together.

The reality is that no pharmacist succeeds alone.

Behind every successful pharmacist is often a network of colleagues, mentors, educators, friends, and professional organisations that have provided encouragement, guidance, and opportunities along the way. As young professionals, we benefit immensely from sharing knowledge, experiences, and resources with one another. When one pharmacist grows, the profession grows alongside them.

The concept of a "new age" Youth Day therefore extends beyond commemorating the past. It challenges us to consider how today's youth can shape the future. For young pharmacists, this means embracing leadership regardless of job title or years of experience. Leadership can be found in advocating for patients, supporting colleagues, mentoring students, participating in professional organisations, and contributing innovative ideas that strengthen healthcare delivery.

It also means recognising that collaboration is essential for addressing the challenges facing our profession. Whether working in community pharmacies, hospitals, industry, academia, regulatory sectors, or public health, pharmacists share a common goal of improving health outcomes and advancing the profession. By working together rather than in silos, we can create stronger support systems and unlock new opportunities for professional growth.

As we commemorate 50 years since the events of 1976, we are reminded that meaningful change often begins with young people who are willing to engage, participate, and support one another. The pharmacists of today have inherited a legacy of courage, determination, and hope. The responsibility now rests with us to continue building a profession that is inclusive, innovative, and responsive to the needs of society.

For the YPG, Youth Day is not only a celebration of young people but also a reminder of the collective strength that exists within our profession. Every conversation, mentorship relationship, collaborative project, and act of support contributes to a stronger pharmacy community.

This Youth Month, let us remember that while our individual journeys may differ, our success is deeply interconnected. We need one another to learn, to grow, to lead, and to overcome challenges. Just as the youth of 1976 demonstrated the power of unity in pursuit of a better future, young pharmacists today have the opportunity to shape the future of pharmacy through collaboration, shared purpose, and mutual support.

The next chapter of pharmacy in South Africa will be written by a generation that understands that leadership is not about standing alone, it is about moving forward together. As we honour the past and look toward the future, may we continue to strengthen the connections that unite us and inspire the change we wish to see within our profession and our communities.

Life after community service: Continuing the conversation through the PSSA YPG podcast

Thinavhuyo Musekene

The transition from community service into the next phase of a pharmacy career is often accompanied by a mixture of excitement, uncertainty, and anticipation. While completing community service marks an important professional milestone, many young pharmacists are left wondering: What comes next?

This important question is explored in the PSSA Young Pharmacists' Group (YPG) podcast, *Life After Community Service*. This podcast series platform creates opportunities for meaningful discussions around career development, professional growth, leadership, and the evolving role of pharmacists in South Africa.

Through engaging conversations with guest speakers and pharmacy professionals, the podcast provides valuable insights into career planning, employment opportunities, networking, mentorship, and professional development. The discussions address some of the most common concerns faced by pharmacists entering the workforce while offering practical guidance on navigating the transition from community service to the next stage of professional practice.

One of the key messages emerging from the podcast is that career success after community service requires intentional planning. The speakers highlight the importance of developing a professional profile that extends beyond academic achievements. Strong communication skills, adaptability,

leadership qualities, and a commitment to lifelong learning are identified as attributes that can help young pharmacists stand out in a competitive job market.

As the pharmacy profession continues to evolve, access to practical guidance and shared experiences becomes increasingly important. The *Life After Community Service* podcast provides an opportunity for early-career pharmacists to learn from one another, explore new perspectives, and gain confidence in navigating their professional journeys.

Young pharmacists, interns, and pharmacy students are encouraged to engage with the podcast and become part of the conversation. The podcast is available on the PSSA YouTube platform with links for episodes distributed through the newsletter, and forms part of the YPG's growing portfolio of initiatives designed to support and inspire the next generation of pharmacy professionals.

Completing community service is not the end of the journey, it is the beginning of a career filled with opportunities for growth, leadership, and meaningful contribution to healthcare. Through conversations such as those featured on the Podcast, young pharmacists are reminded that the future of the profession is theirs to shape.

**Feel free to reach out to us at | Email: ypg@pssa.org.za | Facebook: Young Pharmacists' Group of PSSA | Instagram: @pssaypg
Linkedln: Young Pharmacists' Group of PSSA
Young pharmacists – connected, engaged, empowered and inspired!**

A sore throat, not a sore point: evidence-based management of acute tonsillitis

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Abstract

Acute tonsillitis is one of the most common conditions encountered in primary care and places a significant burden on healthcare services. Although the condition is predominantly caused by self-limiting viral infections that require minimal pharmacological intervention, it is frequently misdiagnosed as a bacterial infection, resulting in unnecessary antibiotic prescribing. This inappropriate use of antibiotics contributes to the growing global challenge of antimicrobial resistance (AMR). Healthcare professionals play a critical role in promoting antimicrobial stewardship (AMS) by reducing unnecessary antibiotic use and implementing evidence-based strategies for providing symptomatic relief. Effective management of acute tonsillitis should focus on alleviating key symptoms, including pain, fever, and inflammation, through appropriate pharmacological and non-pharmacological interventions. Furthermore, patient-centred communication regarding the risks and benefits of antibiotic therapy, as well as alternative treatment options, is essential to support informed decision-making and responsible prescribing practices. This clinical review examines the current evidence for the symptomatic management of acute tonsillitis in primary care and highlights practical approaches that support optimal patient outcomes while advancing AMS efforts.

Keywords: acute tonsillitis, antibiotics, antimicrobial resistance, prescribing, symptomatic management

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Introduction

Overview of tonsillitis

Tonsillitis is an upper respiratory tract infection (URTI) characterised by inflammation of the palatine tonsils, which are lymphoid tissues situated in the lateral oropharynx between the palatoglossal and palatopharyngeal arches. These structures play an important role in immune surveillance and defence against airborne infections.^{1,2} Clinically, tonsillitis typically presents with sore throat, fever, odynophagia, pharyngeal erythema, tonsillar hypertrophy, malaise, and headache.^{2,3} The condition predominantly affects children older than two years (typically in children aged 4–8 years) and young adults (typically between 15 and 25 years of age),⁴ often resulting in school and work absenteeism.^{3,5} Although most cases are self-limiting, untreated streptococcal infections may lead to serious complications, including peritonsillar and parapharyngeal abscesses, acute rheumatic fever, and post-streptococcal glomerulonephritis.^{2,6} Consequently, acute tonsillitis remains an important public health concern due to its frequency, potential for recurrence, impact on quality of life, and risk of complications.⁷

Beyond its clinical impact, tonsillitis imposes a substantial burden on healthcare systems through outpatient consultations, emergency department visits, and hospital admissions.⁸ Globally, tonsillitis accounts for approximately 1.3% of outpatient consultations.² In the United Kingdom, 70 658 hospital admissions related to tonsillitis were reported during 2023–2024, with an estimated hospital bed cost of £901 per admission, highlighting the substantial economic burden associated with the condition.⁸

Similarly, a 2023 study from the United States estimated the annual cost of paediatric bacterial tonsillitis to range between \$224 million and \$539 million, including indirect costs resulting from parental work absenteeism.⁹ Collectively, these findings highlight the significant health care and socioeconomic burden imposed by acute tonsillitis worldwide.¹⁰

Aetiology and pathophysiology

The palatine, adenoid, lingual, and tubal tonsils collectively form Waldeyer's ring, a circular arrangement of mucosal-associated lymphoid tissue (MALT) within the pharynx.¹¹ This strategically positioned lymphoid structure serves as a primary site for antigen sampling and immune surveillance of inhaled and ingested pathogens.¹² As part of the first line of defence, the tonsils function as an immunological barrier by initiating immune responses against invading microorganisms.¹¹ The immunological activity of Waldeyer's ring is particularly pronounced during childhood, when frequent exposure to environmental pathogens stimulates the development of adaptive immunity.¹³

When microorganisms penetrate the tonsillar epithelium, they are engulfed and processed by antigen-presenting cells (APCs), including macrophages and dendritic cells.¹² These cells subsequently present antigens to B- and T-lymphocytes, activating both humoral and cell-mediated immune responses.¹¹ T-lymphocytes within the extrafollicular regions of the tonsils release pro-inflammatory cytokines, including tumour necrosis factor-alpha (TNF- α), interferon-gamma (IFN- γ), and interleukin-2 (IL-2), which coordinate the recruitment and activation of multiple

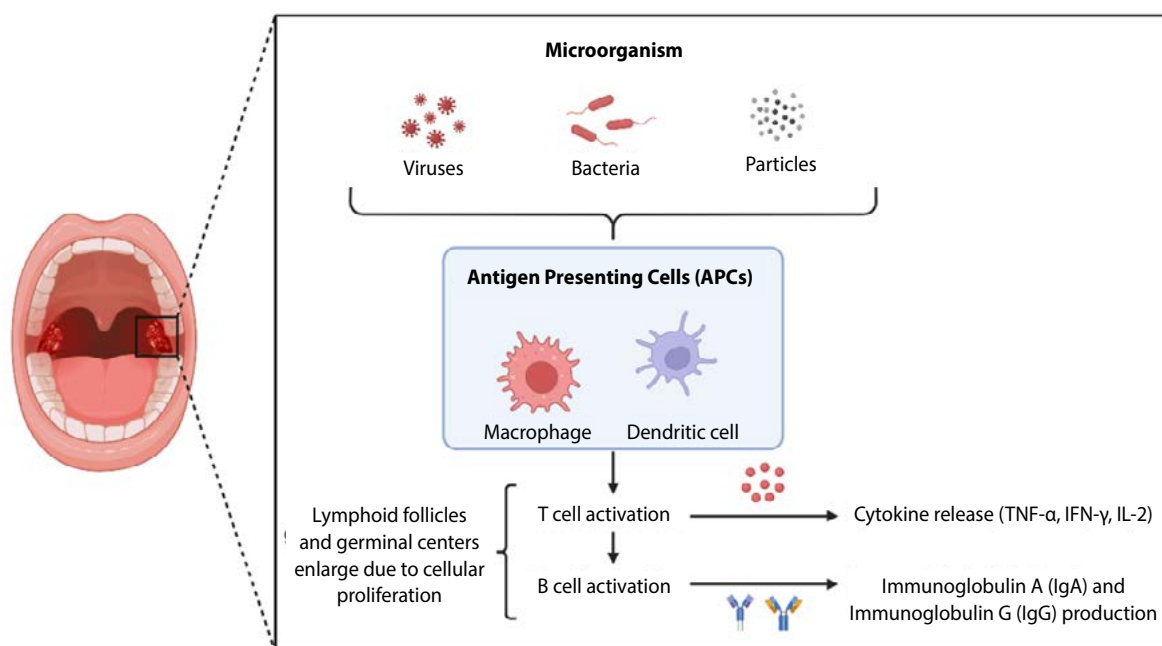


Figure 1: Overview of the immune reaction of the lymphoid tissue of tonsils in response to an antigen. The clinical presentation is a consequence of lymphocytic proliferation and cytokine release. This figure was created with BioRender.com.

immune cells from both the innate and adaptive immune systems.¹⁴ Concurrently, terminally differentiated B-lymphocytes produce immunoglobulin A (IgA) and immunoglobulin G (IgG), which contribute to immune surveillance and inhibit microbial adherence to host tissues.¹² This immune activation results in cellular proliferation, enlargement of lymphoid follicles and germinal centres, and subsequent tonsillar hypertrophy.^{12,15} Despite these protective mechanisms, pathogens may persist and proliferate within the epithelial crypts of the tonsils, ultimately leading to the development of acute tonsillitis and its associated clinical manifestations.¹² Figure 1 illustrates the immune response to tonsillar infection and its symptomatic consequences.

The clinical features of tonsillitis arise largely from the local and systemic inflammatory responses triggered by infection.¹⁶ Cytokine release from activated lymphocytes promotes inflammation, giving rise to symptoms such as pain, fever, and chills.^{13,14} Although acute tonsillitis primarily affects the palatine tonsils, inflammation may also involve the adenoid and lingual tonsils.¹¹ Sore throat results from the action of inflammatory mediators, particularly prostaglandins and bradykinin, on sensory nerve endings within the pharyngeal mucosa. Bradykinin increases vascular permeability, promotes tissue oedema, and directly stimulates pain fibres,¹³ while prostaglandins are involved in inflammation, leading to redness, swelling, and pain.¹⁷ Fever and chills occur as part of the systemic host response to infection and are mediated by pyrogenic cytokines, notably interleukin-1 (IL-1) and interleukin-6 (IL-6), which act on thermoregulatory centres within the hypothalamus.¹⁸ Systemic cytokine release also contributes to sickness behaviour, such as malaise and lethargy, which often adds to the patient missing school or work days.¹³

Viral and bacterial causes

Between 70% and 95% of cases are attributed to viral causes,² specifically adenovirus, influenza, Epstein-Barr virus, human herpesvirus and enteroviruses in children, while adult cases are due to coronavirus and rhinovirus.¹⁹ Bacterial pathogens, typically Group A beta-haemolytic streptococcus (GAS), *Staphylococcus aureus*, *Streptococcus pneumoniae* and *Haemophilus influenzae*¹⁹ account for 15% to 30% of cases in children and less than 15% in adults.²

Clinical presentation and diagnosis

Signs and symptoms

Clinically, the disease manifests as a sore throat, odynophagia, lymphadenopathy and fever, with malaise, nausea and vomiting being fewer common signs and symptoms.²⁰ Viral infection leads to oral ulcers, hoarseness, rhinorrhoea, conjunctivitis, rash and a non-productive cough.²¹ Bacterial infection from *Streptococcus* often leads to complications, such as tonsillar hypertrophy, peritonsillar abscess (PTA), acute rheumatic fever and tonsillar exudate.²

Diagnosis

Diagnosis is based on patient history, assessment of symptoms, and laboratory tests. Clinically, otorhinolaryngological examination⁹ and physical assessment for fever, sore throat with painful swallowing, pharyngeal erythema with or without tonsillar exudates, and painful cervical adenopathy are performed, although these parameters cannot always discern between bacterial and viral aetiologies.^{7,21}

Throat swabs and serological tests are used to establish bacterial or viral aetiology.²² Rapid antigen detection tests (RADTs), nucleic acid amplification tests (NAATs) or the antistreptolysin O titre may be sensitive and faster alternatives to identify bacterial aetiology.^{22,23} RADT can be employed after obtaining a pharyngeal tonsillar swab, followed by a bacterial culture test if results are negative despite high suspicion of bacterial infection.²⁴ The antistreptolysin O titre is a serological investigation where the increase in antistreptolysin O serves as an indication of streptococcal infection.²⁵ Blood tests or endoscopies are not routine in primary care.⁷

Given the difficulty in determining the aetiology and the rising trends in AMR, diagnostic approaches are evolving. Most cases in the paediatric population are attributable to viruses, and accurate and differential diagnoses prevent unnecessary antibiotic prescriptions.²³ Hence, culture swabbing alone is not the best method for determining the correct aetiology. Clinical scoring systems have emerged as comprehensive investigative tools in primary care, with the advantage of reducing laboratory testing costs and labour and reducing antibiotic prescriptions.²¹

Clinical scoring systems

Endorsed by the Centers for Disease Control and Prevention (CDC) and the American College of Physicians-American Society of Internal Medicine (ACP-ASIM),²⁶ the Centor criteria help clinicians distinguish GAS from viral causes and improve antibiotic prescribing practices to alleviate symptoms.^{26,27} Significant in primary care, it is a simple scoring system that allows physicians to determine whether a sore throat is caused by GAS. One point is allocated to each of the following: fever, tonsillar exudate, tender anterior cervical lymphadenopathy, and absence of cough. A high score corresponds to greater probability of streptococcal infection.⁷ ²¹ The FeverPAIN score assesses five variables linked to GAS: fever, purulence, inflammation of tonsils, absence of cough, and doctor visit within three days of symptom onset.²¹ The Mclsaac score is a modified version of the Centor criteria, which takes patient's age into account.²⁶

Management and treatment

Treatment guidelines for acute tonsillitis are recommended based on the severity of the disease, diagnostic scoring, and patient symptoms. Acute sore throat usually resolves within 10–14 days, regardless of the cause, and does not require intensive treatment.²¹ The majority of cases are viral and self-limiting; hence, only supportive care may be needed.²

Symptomatic management

Self-limiting conditions causing sore throat require symptomatic management through hydration therapy, rest, and saltwater gargles.^{2,21} Non-pharmacological interventions include non-medicated lozenges and mouthwashes.²⁸ Medicated lozenges, local analgesics, anti-inflammatories, antipyretics, and corticosteroids can be administered to reduce pain, fever, and inflammation.² Antibiotics are considered in cases of bacterial

infections caused by GAS² and if symptoms persist and a high score is obtained on the Centor, Mclsaac, or FeverPAIN criteria.⁹ Table 1 provides a summary of antibiotics, topical therapies, analgesics, antipyretics, anti-inflammatory, and corticosteroid drugs used in the treatment and management of acute tonsillitis.

Antibacterial therapy

Antibiotics

Antibiotics are used to shorten disease duration and prevent complications caused by bacterial organisms, such as peritonsillar abscess and acute rheumatic fever.² The CDC and ACP suggest antibiotic usage if the aetiology is confirmed to be GAS through differential diagnosis.² According to the National Institute for Health and Care Excellence (NICE) guideline published by the United Kingdom, it is advisable to avoid antibiotics when the Centor score lies between 0–2 and the FeverPAIN score is 0 or 1.²⁹

Penicillin remains the first-choice drug.⁹ It is cheap, well tolerated, has a narrow spectrum of activity, with little to no adverse effects and reduces the incidence of rheumatic fever.²¹ Oral Penicillin V (phenoxymethylpenicillin-potassium) is recommended for children and adolescents for 5–7 days, based on body weight.⁹ The standard dosage for adults and adolescents weighing more than 30 kg is 500 mg, twice or thrice daily for 10 days.²¹ A recent clinical study assessing dosages reported mild adverse effects in patients treated with penicillin V for sore throat.³⁰ Benzathine penicillin (Pen G) can be administered intramuscularly, with a single dose of 1.2 million units.²¹

An alternative is amoxicillin or amoxicillin-clavulanate for ten days dosed at 50 mg/kg, it absorbs readily and has longer plasma half-life with low protein binding, with low adverse effect profile.^{2,21,31} However, suspensions are preferred in children due to their pleasant taste and ease of administration.²¹ In cases of penicillin intolerance, oral doses of macrolides (clarithromycin, erythromycin, azithromycin), cephalosporins (cephalexin) or clindamycin are used as secondary options.⁹

Standard guidelines suggest 7.5 mg/kg/dose twice daily of clarithromycin for 10 days or a course of 12 mg/kg azithromycin followed by 6 mg/kg for five days.^{21,23} Erythromycin is a macrolide alternative for penicillin allergy when pregnant; 250–500 mg four times daily, or 500–1000 mg twice daily for five days is recommended by the NICE,²⁹ or 40 mg/kg body weight divided into two single oral doses for five days.⁹ The macrolides are well tolerated with mild adverse effects.³²

A 7 mg/kg/dose clindamycin three times daily is an option for patients resistant to macrolide antibiotics or for children with anaphylactic penicillin allergy.^{21,23} Amongst cephalosporins, cephalexin can be prescribed to children with non-anaphylactic penicillin allergy; 40 mg/kg, divided into two daily doses and given over a 10-day period.²³ Another option is cefadroxil, prescribed 30 mg/kg daily with two doses for children, and 1 g once or twice daily for adults over a 10-day period.³³ Cephalosporins may cause gastrointestinal disturbances; they have a similar mechanism of action to beta-lactams; hence, allergic reactions may still occur.²¹

Topical therapies: lozenges and oral sprays

Topical therapy delivers active ingredients directly to the inflamed site and reduces the risk of toxicity when compared to systemic administration,³⁴ and these includes local anaesthetics and antiseptics formulated in gargle solutions, throat sprays and lozenges.³⁵ Lozenges are advantageous due to their ease of administration, prolonged contact time at the site of action, and ability to reach the lower pharyngeal cavity and tonsils via salivary transport.³⁶ Sucking lozenges stimulates production of saliva; it promotes lubrication and soothing of irritated throat lining.³⁴

Medicated lozenges contain benzocaine, flurbiprofen, or hexylresorcinol. The effectiveness of pain relief is not strong, and adverse effects include taste disturbances, nausea, numbness, and dry mouth.²⁹ Over-the-counter (OTC) lozenges for acute sore throat also include Amylmetacresol and 2,4-Dichlorobenzylalcohol (also known as Strepsils[®]) with additives for flavour and lidocaine. This formulation is considered safe for uncomplicated cases seeking local treatment options for pain relief.³⁷ According to the South African Health Products Regulatory Authority (SAHPRA), it should be administered only to children above the age of six. One lozenge should be consumed at two- to three-hour intervals.³⁸ Another local anaesthetic is ambroxol, a sodium channel blocker which alleviates inflammation and pain, preventing unnecessary antibiotic prescriptions. A clinical study using ambroxol reported several minor adverse effects, likely attributed to complications of the underlying disease or symptom progression.³⁹ A study by Dao et al.³⁴ supports the effectiveness of ectoine and hyaluronic acid lozenges in reducing swallowing pain and cough and reducing hoarseness within seven days of treatment.

Oral sprays are more efficacious in coating the oropharynx than mouthwashes.⁴⁰ Topically formulated benzydamine hydrochloride (Diffiam[®]) has been proven effective for the symptomatic management of oropharyngeal conditions as either a 0.3% spray or 3 mg lozenges, both with minimal to no adverse effects.^{40,41} A chlorhexidine/lidocaine spray (xylocaine) has been used for a long time, and its effectiveness is largely attributed to its bactericidal and bacteriostatic properties, coupled with the oral substantivity of chlorhexidine. Lidocaine serves as a local analgesic with proven clinical properties; it is generally administered by a healthcare professional and carries risk of hypersensitivity.^{42,43}

Analgesics, antipyretics and anti-inflammatories

Oral analgesics are standard of care used to alleviate symptoms, reduce fever, treat headaches and throat pain; these are paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs): diclofenac potassium, ibuprofen and aspirin.^{7,9,29} Patients presenting with systemic symptoms like arthralgia, headache and chills are recommended to seek over-the-counter NSAIDs, rather than short-acting lozenges or topical therapies.³⁹ Although caution should be taken in case of dehydration due to nephrotoxicity, rehydration therapy is implemented in conjunction with analgesic drugs.⁷ Except diclofenac, most oral analgesics for sore throat and pain relief are OTC drugs.²⁹ Paracetamol is effective in reducing

discomfort after a single dose or over two days of continuous use.⁴⁴ Opioid metabolites such as tramadol or codeine (also OTC) are contraindicated in patients with respiratory conditions, especially airway depression, and are not recommended in children.⁷ The World Health Organization (WHO) recommends non-opioid analgesics like paracetamol for mild pain and weak-acting opioid analgesics for moderate pain.⁴⁵

Corticosteroids

Corticosteroids, used as adjuvants, resolve symptoms and reduce inflammation,⁴⁶ offering short-term relief from pain and odynophagia.² They are regularly used by patients with sore throat or exudative pharyngitis caused by similar infectious agents.⁴⁷ However, their usage needs to be monitored, and risk/benefit evaluation should be conducted in immunocompromised or diabetic patients.² Dexamethasone is the standard for pain relief in acute exudative pharyngitis in adults with three or four points on the Centor criteria, administered orally or intramuscularly (IM), usually as a single dose of 8 mg or 10 mg.^{21,47} An alternative is oral prednisone or betamethasone, although they are less effective. IM administration has a rapid onset of action; hence, it is appropriate for emergencies, whereas oral corticosteroids are advantageous in primary care.⁴⁷

Complementary and alternative medicines (CAMs)

Some patients seek complementary and alternative medicines (CAMs)² or integrative medicine (IM).³⁵ In ayurvedic medicine, Kanchnara Guggulu and Pratisarana of Tankana-Madhu have demonstrated safety and efficacy in children, with significant reduction in pricking pain, burning sensation, fever, inflammation and additional signs such as redness of tonsils, lymphadenopathy, dysphagia, halitosis, anorexia and hoarse voice.⁴⁸ Tonzolyt[®], a homoeopathic drug containing several active ingredients (Atropa belladonna D4, Calcarea phosphoricum D4 and more) possesses anti-inflammatory and pain relief qualities.⁴⁹

Herbal medicines with significant symptomatic improvement, especially anti-inflammatory response and fever reduction, include EPs[®] 7630 (Umckaloabo), BNO 1030 extract (Imupret[®]), essential oils (thyme and marjoram) and carvacrol.⁵⁰⁻⁵² Hypothetically, EPs[®] 7630, an extract of *Pelargonium sidoides*, is considered to reduce microbial adherence to tonsils; it has been shown to be effective for tonsillopharyngitis in children, with few side-effects.³⁵ BNO 1030 is a concoction of seven plants (marshmallow root, chamomile flowers, horsetail herb, walnut leaves, yarrow herb, oak bark and dandelion herb) and has shown effectiveness when combined with acetaminophen and benzydamine hydrochloride oral spray.³⁵

Owing to its antimicrobial properties, honey is considered a 'lay' remedy for URTIs and a natural alternative to its medical counterparts. Studies have shown that honey reduces cough frequency and severity, with mild nausea as a side-effect. There is little risk of allergic reactions, and it is a low-cost, readily accessible commercial product, leading to general acceptability among

Table 1: Medicinal products used to treat GAS infection or reduce symptoms in patients with acute tonsillitis

Drug class	Subtype	Medication	Indication	Dosage and formulation	Adverse effects
Antibiotics ^{2,3,9,23,29,33,54, 55}	Beta lactam	Penicillin V	GAS infection	- Children: 0.05–0.1 million IU/kg body weight/day divided into three single oral doses for 5–7 days - Adolescents: phenoxymethylpenicillin-potassium 0.8–1.0 million IU (or phenoxymethylpenicillin benzathine 100,000 IU/kg body weight) orally three times daily for 5–7 days	Diarrhoea, nausea, and vaginal discharge or itching
		Amoxicillin		50 mg/kg once daily for 10 days	Diarrhoea, nausea or rash
		Clarithromycin		- Children: 15 mg/kg body weight/day divided into two single oral doses for 5 days - Adolescents: 250–500 mg orally twice daily for 5 days	Diarrhoea, nausea or rash
	Macrolide	Erythromycin		- Adolescents: 40 mg/kg body weight divided into 2 single oral doses for 5 days 250–500 mg four times daily, or 500–1 000 mg twice daily for 5 days	Diarrhoea, nausea or rash
		Azithromycin		12 mg/kg azithromycin followed by 6 mg/kg for 5 days	Diarrhoea, nausea or rash
		Clindamycin		- Children: 7 mg/kg/dose three times daily - Adolescents: 20 mg/kg body weight/day divided into three single oral doses for 5 days	Diarrhoea
Antiseptic ^{27,38}	Lincosamide			40 mg/kg, divided in 2 daily doses over a 10-day period	Diarrhoea, nausea or vomiting
		Cephalexin			Hypersensitivity
	Cephalosporins				Gastrointestinal disturbance
		Cefadroxil			Hypersensitive
	Lozenge	Strepsils [®]	Short term pain relief	Adults and children above 6 years: dissolve one lozenge slowly in the mouth every 2–3 hours	Hypersensitivity, abdominal pain, nausea, oral discomfort or rash
	Mucolytic agent	Ambrosept [®] (ambroxol)	Pain relief and inflammation	Adults and children above 10–12 years: 20 mg–30 mg thrice daily	Oral hypoaesthesia, dysgeusia, dry mouth, skin rash, nausea, insomnia, sweating, pharynx oedema, migraine, tremor and pharyngitis
Topical NSAID ^{40,41}	Local analgesic and anti-inflammatory	Benzylamine Hydrochloride (Diffiam [®])	Short term pain relief	0.3% oromucosal spray - Children under 6: 1 puff per 4 kg body weight up to a maximum of 4 puffs every 1½ to 3 hours - Children between 6–12: 4 puffs, every 1½ to 3 hours - Adults: 4 to 8 puffs, every 1½ to 3 hours	Hypersensitivity, oral disturbance or rash
		Lidocaine	Short term pain relief	Administered by the health care professional	Hypersensitivity or rash
Non-opioid analgesics and antipyretics ^{7,29, 57,58,59}	Acetaminophen	Paracetamol	Pain and fever	1g IV - Children: ½–1 tablet orally repeated every 4–6 hours - Adults: 1–2 tablets orally repeated every 4–6 hours	Nephrotoxicity, hypersensitivity, rash, or fainting
		Ibuprofen	Pain, fever and inflammation	- Single dose: 1 400 mg tablet - Maximum daily dose: 3 tablets per day	Headaches, gastrointestinal disturbances, renal and liver toxicity
	NSAID	Aspirin	Pain, fever and inflammation	Adults: 1–2 tablets daily every 4 hours	Hypersensitivity, fever, gastrointestinal disturbances
		Diclofenac potassium	Pain relief	50 mg PO or 75 mg PR	Cardiovascular risk

[S1] Strepsils®

Intensive

Lozenge & Spray

Flurbiprofen 8,75 mg

RAPID

ANTI-INFLAMMATORY ACTION

FROM 20 SECONDS*^{1,2}

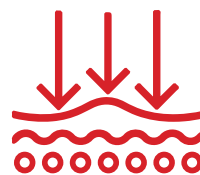
Benefits of Flurbiprofen



Relieves pain in
1 minute³



Long lasting relief
for up to **6 hours**^{4,5}



Penetrates deep down
into the throat tissue⁶

AVAILABLE IN TWO FORMULATIONS

Strepsils Intensive Spray



WHO?

- + Adults 18 years and older who require short term symptomatic relief of acute sore throat⁷

WHEN?

- + One dose (three sprays) every 3-6 hours as needed; no more than five doses in 24 hours⁷
- + Use for a maximum of 3 days⁷

Strepsils Intensive Lozenges



WHO?

- + Adults and children 12 years and older who require relief of pain of sore throats⁸

WHEN?

- + One lozenge every 3-6 hours as needed; no more than five lozenges in 24 hours⁸
- + Use for a maximum of 3 days⁸
- + Use whenever symptoms present⁸

*In-vitro study.

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FLURBIPROFEN 8,75 mg

[S1] Strepsils Intensive Spray 8,75 mg throat spray. Reg. No. 50/16/0351. Each metered dose (3 sprays) contains: 8,75mg flurbiprofen. [S2] Strepsils Intensive Lozenges. Reg. No.: 35/16/0015. Each lozenge contains 8,75 mg flurbiprofen. Business name and address of the holder of the certificate of registration: Reckitt Benckiser Pharmaceuticals (Pty) Ltd., 8 Jet Park Road, Elandsfontein, 1601. For full prescribing information refer to the Professional Information approved by the Medicines Regulatory Authority. Customer Care Line: 0861 11 11 00. RT-M-wcE7dt



Some products may not be available in your market.

	Botswana	Zimbabwe	Zambia	Namibia
Strepsils Intensive	BOT1402602 (S4)	2014/3.1/4889 (P)	133/020 (GS)	13/16/0177 (NS1)
Strepsils Intensive Spray	BOT2500036 (S3)	2025/20.3.3/7043 (P)	ZAMRA-HM-25-250 (P)	



Table 1: Medicinal products used to treat GAS infection or reduce symptoms in patients with acute tonsillitis

Drug class	Subtype	Medication	Indication	Dosage and formulation	Adverse effects
Opioid analgesics ^{60,61}	Weak opioid	Tramadol	Pain relief	• Adults: 50 mg–100 mg per instance (monitor effect over 4–8 hours)	Hypersensitivity, dizziness, nausea, headaches, fatigue, sweating, gastrointestinal disturbances
		Codeine		• Adults: 30 mg to 60 mg every six hours	Hypersensitivity, drowsiness, constipation, sweating
Corticosteroids ^{2,47,62,63}	Glucocorticoid	Dexamethasone	Pain relief	• Orally or IM • 8 mg or 10 mg	Hypersensitivity, gastrointestinal disturbance, neurologic effects
		Prednisone		• Oral	Hypersensitivity, gastrointestinal disturbance, risk of blood clot formation

patients and serving as an optimal alternative.⁵³ Gargling is another home remedy. Hypertonic saline solution irrigates and cleanses the throat; it alleviates soreness and reduces reliance on OTC medication.³⁴

Driving antimicrobial stewardship with evidence-based management

The WHO has classified AMR as a major public health threat, largely owing to the misuse and overuse of antimicrobials, which has led to the emergence of drug-resistant pathogens. Threatening medical treatment and gold-standard antimicrobials, the rise of AMR is exerting significant socio-economic pressures.⁶⁴ According to the World Bank, it is estimated that by 2050, AMR would incur up to US\$ 1 trillion in healthcare costs, and by 2023, between US\$ 1 trillion and US\$ 3.4 trillion in gross domestic product (GDP) losses per year.⁶⁵ Antibiotic usage, especially when most cases are attributed to viral causes, is concerning due to increased resistance in the community, especially paediatric practice, which sees the highest number of cases.^{35,46} Despite little evidence of benefit for the condition, the antibiotic prescribing rate for sore throat is high.⁴⁶ Reliance on prescribed antibiotics for URTIs in primary care is accelerating AMR.⁵³

Evidence-based management is a cornerstone of driving antimicrobial stewardship (AMS) practice in primary care through collaboration among healthcare professionals and the role of pharmacists in expanding patient education and improving prescribing practices.⁶⁶ An appropriate diagnosis would establish disease aetiology. Diagnostic assessments using the Centor criteria, McIsaac criteria, and FeverPAIN scoring allow clinicians to estimate the probability of bacterial tonsillitis, rule out viral causes, identify low-risk patients, and establish an appropriate treatment plan.^{9,33} Antibiotics have been shown to be effective in treating GAS infections when the Centor score is 3 or 4 and the FeverPAIN score is 4 or 5.²¹ Daniels et al. suggested that point-of-care testing (POCT) should be performed after the Centor algorithm is used, and that a positive result should prompt the clinician to prescribe antibiotics. While POCT incurs consumable and setup costs, it also reduces antibiotic costs and facilitates targeted prescribing, with a wider impact on health systems.⁶⁷

According to the NICE guidelines on AMS, prescribers should follow local guidelines, elect the shortest courses coupled with appropriate dosages, and consider the risk of AMR. It further encourages clinical assessment, POCT testing in primary care, and microbiological specimen identification in cases of recurring or persistent infections.⁶⁸ The guidelines emphasise communication, continuous education, and feedback to improve prescribing practices. Alternative treatment options, such as self-care, OTC products, or non-pharmacological interventions, should be communicated to the patient, along with the benefits and risks of antimicrobial use. Immediate prescription is not adequate for self-limiting conditions.⁶⁸

A delayed prescription approach has emerged in clinical guidelines for low-risk cases.⁹ This could be due to potential challenges such as gastrointestinal effects, healthcare costs, and antibiotic resistance.² Herein, the clinician advises when or whether antibiotics should be taken, rather than immediate use, with the expectation that symptoms will pass.^{69,70} This strategy builds two-way trust between patient and clinician and empowers and educates users on responsible antibiotic use.⁶⁹

In case of GAS infection, narrow-spectrum antibiotics (penicillin, cephalosporins and macrolides) (Table I) should be prescribed, especially in cases of recurring tonsillitis.³³ Comprehensive laboratory testing is needed in cases of GAS susceptibility, especially when non-beta-lactam agents are prescribed.²³ Sulphonamides, fluoroquinolones and tetracyclines should not be used.²³ Recurring and chronic cases, community outbreaks and family histories, as well as seasonal epidemiology, need to be monitored to aid in reducing excess antibiotic exposure and treatment costs.²³

Based on evidence in the literature, the treatment algorithm in Figure 2 aims to provide guidelines for approaching self-limiting conditions such as acute tonsillitis, while considering responsible prescribing practices and driving AMS in primary care.^{7,9,21,23,33,35,44,71}

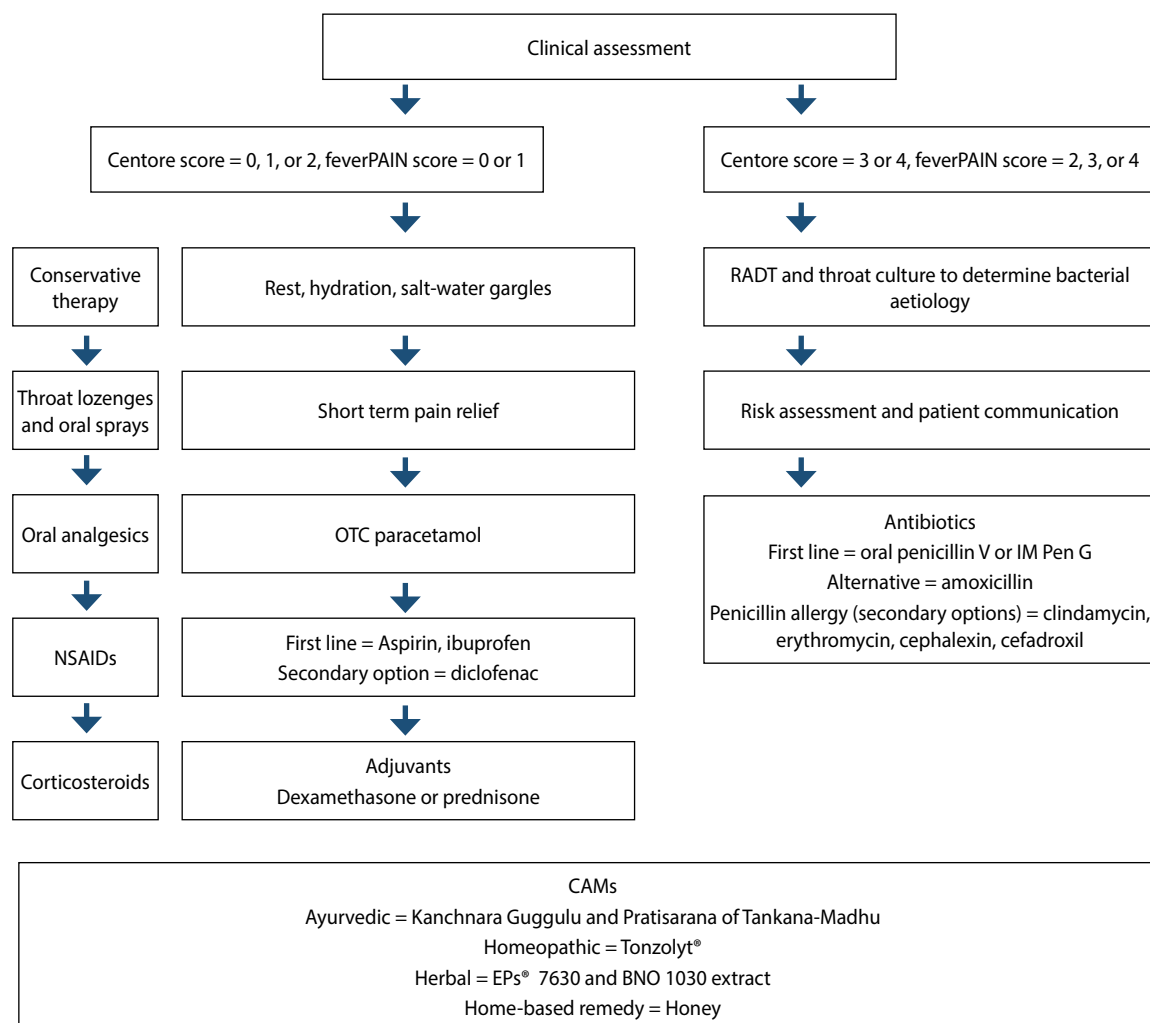


Figure 2: Treatment algorithm for the management of acute tonsillitis in primary care. A clinical assessment is recommended, followed by confirmatory culture tests before antibiotics are prescribed. Symptomatic management largely relies on topical therapies, oral analgesics, NSAIDs, and corticosteroids, whereas CAMs provide an alternative which may be preferred by some patients.

Conclusion

Acute tonsillitis presents a significant healthcare burden, especially in paediatric primary care. The aetiology could be viral or bacterial; hence, accurate diagnosis using clinical assessment tools is necessary before implementing a treatment plan. Symptomatic management for this self-limiting condition involves pain relief and the reduction of fever and inflammation using conventional therapy, topical lozenges, oral sprays, oral analgesics, antipyretic and anti-inflammatory agents, and corticosteroids as adjuvants. In CAMs, patients can opt for ayurvedic, homeopathic, herbal, and other natural products to self-manage their condition. Owing to the emerging public health concern of AMR, clinicians should consider diagnostic tools, benefit-risk assessments, and alternative therapies when prescribing antibiotics. Patient communication and education by clinicians and pharmacists, especially regarding the risks of antibiotic overuse and possible alternative therapies, could significantly reduce the threat of resistance.

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Optimising prevention of shingles with vaccination: considerations for pharmacists

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Abstract

Herpes zoster or shingles is caused by the reactivation of latent varicella-zoster virus (VZV) following primary varicella (chickenpox) infection. Although shingles can occur at any age, it is predominantly a disease of older adults, with incidence increasing substantially from 50 years of age due to age-related decline in VZV-specific cell-mediated immunity. In South Africa, the burden of disease is further amplified by the high prevalence of HIV infection and the growing population of older adults living with chronic medical conditions. Shingles is associated with significant morbidity, including acute neuropathic pain, post-herpetic neuralgia, ophthalmic disease, neurological complications, and reduced quality of life. Prompt diagnosis and initiation of antiviral therapy remain important for reducing symptom severity and preventing complications. However, advances in vaccination have shifted the focus from treatment to prevention, with recombinant zoster vaccines having demonstrated high efficacy in preventing shingles and its complications. Pharmacists are uniquely positioned to support comprehensive shingles prevention as part of a life-course immunisation strategy. This review provides an update on the epidemiology, clinical manifestations, management, and prevention of shingles, with particular emphasis on the expanding role of pharmacists in reducing the burden of shingles in South Africa.

Keywords: Herpes zoster, shingles, post-herpetic neuralgia, recombinant zoster vaccine, pharmacist, immunisation, prevention, health communication

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Introduction

Herpes zoster (HZ), commonly referred to as shingles, is a viral disease which results from the reactivation of latent varicella-zoster virus (VZV).¹ Shingles is characterised by a painful skin rash with blisters in a localised area. Other common symptoms include fever, headache and tiredness. Post-herpetic neuralgia (PHN) is one of the most common and chronic complications of shingles.^{1,2} Clinical diagnosis of shingles is usually sufficient, although laboratory tests such as blood testing for VZV-specific IgM antibody or PCR testing of lesion swabs may be used to confirm a diagnosis.³ Early treatment of shingles with antivirals and symptomatic management of the patient, are the cornerstone of management.⁴ However, the introduction of highly effective recombinant zoster vaccines (RZV) has shifted the focus from treatment to prevention.

Virology, pathogenesis and clinical manifestation

The VZV (*human herpesvirus 3, HHV3*) is an enveloped double-stranded DNA virus belonging to the family *Herpesviridae* and subfamily *Alphaherpesvirinae*.⁵ Infection with VZV can lead to two distinct diseases i.e. varicella and shingles. Primary infection with VZV causes varicella (chickenpox), which is an acute, highly contagious disease, common in childhood and characterised by a generalised vesicular rash comprising lesions at various stages of development, distributed over the face, trunk and extremities.^{1,2} Following resolution of the primary infection, VZV establishes lifelong latency within sensory nerve ganglia, where it remains

dormant until potential reactivation later in life as HZ (shingles).^{1,2}

Primary VZV is acquired through inhalation of respiratory droplets or direct contact with fluid from vesicular skin lesions and is among the most highly contagious infectious diseases affecting humans.² Following exposure, the virus initially replicates within the respiratory epithelium before spreading to regional lymph nodes and presents as chickenpox.^{1,2} Systemic dissemination of the virus results in a rash which is characterised by successive crops of lesions at different stages of evolution, including macules, papules, vesicles, pustules, and crusts, which may coexist simultaneously. In some cases, healing lesions may result in residual scarring, particularly following secondary bacterial infection or extensive excoriation.^{1,2}

The incubation period for varicella typically ranges from 10 to 21 days following exposure.^{1,2} Infected individuals are contagious from approximately 1 to 4 days before the onset of the characteristic rash and remain infectious until all vesicular lesions have crusted over and dried completely. This period of infectivity contributes significantly to the high transmissibility of the disease.¹

Following primary infection, VZV establishes lifelong latency within neuronal tissues, including the dorsal root ganglia, cranial nerve ganglia, autonomic ganglia of the enteric nervous system, and, to a lesser extent, astrocytes.^{1,2} During this latent phase, the virus remains dormant and clinically silent, maintained by VZV-specific cell-mediated immunity.^{1,2}

Table I: Clinical stages of shingles^{1,2}

Clinical Stage	Duration	Symptoms
Pre-eruptive stage	2 days	Headache, general malaise and photophobia
Acute eruptive phase	2–4 weeks	Vesicular rash often burst, ulcerate, and eventually dry out. Severe pain which is sometimes unresponsive to nonsteroidal anti-inflammatory drugs (NSAIDs).
Chronic infection	> 4 weeks (may last several months or years)	- Patients experience PHN, dysesthesias, paraesthesia and sometimes shock-like sensations. - PHN pain is disabling and may last for weeks, months or even years after the blisters have healed. - HZ ophthalmicus, disseminated HZ, neurological conditions (meningitis, encephalitis), Ramsay Hunt Syndrome, hearing loss and scarring may occur in some cases.

Shingles occurs when latent VZV reactivates, typically due to waning immunity associated with ageing, immunosuppression, or other host factors.^{1,2,6} Upon reactivation, the virus replicates within the affected sensory ganglion and travels along the corresponding sensory nerve to the skin, resulting in a characteristic unilateral vesicular eruption confined to the affected dermatome.^{1,2,6} This rash is usually accompanied by acute neuropathic pain, which may precede the appearance of skin lesions by several days.^{1,2,6}

Clinically, shingles is characterised by a painful, unilateral vesicular rash that most commonly involves a single dermatome.^{1,2} Although the cutaneous manifestations generally resolve within 2–4 weeks, associated complications may persist for months or even years.^{1,2} The most common and debilitating complication is PHN, a chronic neuropathic pain syndrome that can substantially impair quality of life through persistent pain, sleep disturbance, reduced physical functioning, anxiety, depression, and social isolation.^{1,7}

Beyond its acute manifestations, growing evidence suggests that shingles may be associated with an increased risk of cerebrovascular and cardiovascular events.^{8,9} Studies have reported a transient elevation in stroke risk following VZV reactivation, with one study documenting a 127% increase in the risk of stroke during the first two weeks after disease onset.⁸ Furthermore, reactivation involving the ophthalmic branch of the trigeminal nerve, known as HZ ophthalmicus, may result in serious ocular complications, including keratitis, uveitis, retinitis, and optic nerve involvement, potentially leading to permanent visual impairment or blindness if not promptly diagnosed and treated.¹⁰ Other complications may include secondary bacterial infections, and, in severe cases, disseminated disease, including neurological complications (such as meningitis and encephalitis).^{1,2} Table I summarises the clinical stages of shingles.

Shingles prevalence and high-risk groups

Shingles occurs worldwide and represents a significant public health concern, with approximately one in three individuals developing the disease during their lifetime. The global annual incidence is estimated at 3–5 cases per 1 000 person-years in the general population, increasing substantially with advancing age to approximately 8–12 cases per 1 000 person-years among adults aged 60 years and older.^{6,11,12} The incidence of shingles increases around four-fold in persons over 80 years when compared to persons under 50 years. Because shingles results from the

reactivation of latent VZV acquired during primary varicella infection, its incidence is strongly influenced by age-related decline in cell-mediated immunity (immunosenescence).^{12,13}

In children and young adults, shingles is relatively uncommon and when it occurs, may be associated with underlying severe immunodeficiency, malignancy, or other serious medical conditions.^{11,14} In contrast, among adults, increasing age is the most important risk factor for disease development.¹⁵ Additional risk factors include psychological stress, immunosuppressive therapies, malignancies, chronic medical conditions, and infections associated with immune dysfunction, particularly human immunodeficiency virus (HIV) infection.¹⁴ More recently, cases of shingles have been reported following COVID-19 vaccination, however, current evidence indicates that the benefits of COVID-19 vaccination substantially outweigh any potential risk of VZV reactivation, and a causal relationship has not been conclusively established.^{16,17,18}

In sub-Saharan Africa, and South Africa in particular, the epidemiology of shingles is further influenced by the high prevalence of HIV infection.^{6,11,19} HIV-associated immune suppression significantly increases the risk of VZV reactivation, resulting in a higher incidence of shingles and a tendency for disease to occur at younger ages than is typically observed in Europe and North America.^{6,19} In many African settings, shingles is recognised as an important clinical indicator of underlying immune compromise and may represent one of the earliest manifestations of previously undiagnosed HIV infection.^{6,11}

Transmission

Shingles itself is not contagious and is therefore not transmitted from one person to another.²⁰ However, individuals with active shingles can transmit or spread the virus to susceptible individuals who have never had chickenpox (varicella) or who have not been vaccinated against chickenpox.²⁰ Should this happen, these individuals would develop chickenpox, and not shingles.²⁰ Once chickenpox resolves, they would be at risk for shingles.²⁰ On the other hand, the chickenpox vaccine contains a weakened version of the VZV and can reduce the risk of developing shingles later in life.^{20,21} Studies have shown that children who received the chickenpox vaccine are significantly less likely to develop shingles compared to those who contracted chickenpox naturally.^{20,21}

Transmission of the virus occurs primarily through direct contact with the fluid from the shingles blisters (vesicular lesions).²⁰

Table II: Management strategies for shingles^{4,22}

Strategies	Recommendations for management of shingles
Antiviral therapy	Commonly prescribed antiviral agents include: • Acyclovir: 800 mg orally five times daily for 7 days (given 4 hourly except for the dose scheduled for the middle of the night) • Valacyclovir: 1 000 mg orally three times daily for 7 days • Famciclovir: 250 mg orally three times daily for 7 days Note: Valacyclovir and famciclovir are generally preferred over acyclovir because of their superior oral bioavailability and more convenient dosing schedules, which may improve treatment adherence.
Pain management	First-line treatment options for mild to moderate pain: • Paracetamol 500 mg to 1 g, 4–6 hourly as required (maximum of 4 g in 24 hours) • Nonsteroidal anti-inflammatory drugs (NSAIDs) Patients with severe pain: • Short courses of opioid analgesics e.g. tramadol 50–100 mg 6 hourly Neuropathic symptoms (post-herpetic neuralgia) treatment options: • Tricyclic antidepressants e.g. amitriptyline 10 mg at night • Gabapentinoids e.g. gabapentin, pregabalin
Topical and supportive care	Supportive care measures are important for symptom relief and prevention of secondary bacterial infection. Patients should be advised to do the following: • Keep lesions clean and dry • Avoid scratching affected areas • Maintain good hand hygiene • Cover lesions when appropriate to reduce transmission risk Calamine lotion and cool compresses may provide symptomatic relief from discomfort and pruritus. Topical antibiotics are not routinely indicated unless secondary bacterial infection is suspected.

Once the lesions have crusted over, the risk of spreading the virus is very low.²⁰ To prevent spreading the virus, the lesions should be covered, touching the lesions avoided and good hand hygiene practised.^{20,22} Contact should be avoided with immunocompromised individuals, non-immune pregnant women (who never had chickenpox or the chickenpox vaccine), and newborn infants who may develop severe chickenpox.^{20,22} In contrast, the risk of shingles transmission from individuals who have been vaccinated with the RZV is non-existent because the vaccine does not contain the live virus.¹²

Management of shingles

Optimal management of shingles requires early recognition and diagnosis, prompt management to minimise symptom severity, accelerate recovery, and reduce the risk of complications, particularly PHN, and prevention through vaccination.^{3,4} The primary goals of shingles management include the following:^{3,4,22}

- **Prompt and effective treatment of the acute viral infection:** Antiviral therapy is the cornerstone of treatment and is most effective when initiated within 72 hours of clinical symptoms and rash onset. Early treatment reduces viral replication, accelerates lesion healing, decreases acute pain severity, and may reduce the risk of complications. Antiviral treatment may be administered beyond 72 hours, in patients with ongoing vesicle formation, severe disease, or immunocompromising conditions.^{3,4,22}
- **Adequate control of acute pain and associated symptoms:** Effective pain control is a critical component of shingles management, as acute pain can be severe and may significantly

impair quality of life. A combination of different classes of analgesics is often necessary. Recommended pain management during the acute phase of infection include paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) and/or opioids if the pain is not adequately controlled. Neuropathic pain is best managed with tricyclic antidepressants or gabapentinoids.^{3,4,22}

- **Prevention of complications, particularly PHN:** Appropriate pain management during the acute phase may contribute to improved patient comfort and potentially reduce the risk of persistent neuropathic pain.^{3,4,22}
- **Maintain functional status and quality of life:** Topical and supportive care with calamine lotion and cool compresses may provide symptomatic relief from discomfort and pruritus.^{3,4,22}

Table II provides an overview of the most common management strategies for shingles.^{4,22} Therapeutic decisions are guided by the patient's age, immune status, severity of symptoms, extent of disease, and the presence of complications.³ Patients should be referred to an ophthalmologist if there is ocular involvement with ophthalmic zoster.²² Secondary infection is uncommon. However, if bacterial cellulitis associated with the vesicles is suspected, oral flucloxacillin 500 mg 6 hourly for 5 days is recommended.²²

Rationale for shingles prevention

Because shingles arises from the reactivation of latent VZV, vaccination remains the most effective strategy for enhancing VZV-specific immunity, preventing viral reactivation and reducing the substantial burden of disease and its complications.¹² The benefits of preventing shingles include the following:

- **Preventing painful acute disease and risk of PHN:** Severe neuropathic pain and a painful rash from shingles may significantly affect daily activities, sleep and overall wellbeing. Furthermore, PHN is the most common serious complication of shingles, causing persisting acute pain lasting for months or years after the rash resolves.^{1,2,7,12}
- **Preventing serious complications:** Serious complications of shingles include vision loss from HZ ophthalmicus, neurological disorders such as meningitis and encephalitis, and disseminated disease in vulnerable individuals.^{10,12}
- **Protecting high-risk populations against severe disease:** Older adults and immunocompromised individuals are at increased risk of shingles, recurrent disease, and complications.^{12,13}
- **Preserving quality of life and healthy ageing:** Shingles and its complications can impair physical functioning, psychological wellbeing, social participation, and independence.^{1,7,12,23}
- **Reducing healthcare utilisation and costs:** Shingles often requires medical consultations, antiviral treatment, pain management and hospitalisation, associated with an economic burden on individuals and health systems.¹²
- **Potentially reducing the risk of cardiovascular events:** Evidence suggests that HZ infection may increase the risk of stroke and other cardiovascular events through inflammatory and vascular mechanisms.^{8,9,12,24}
- **Potentially reducing dementia risk:** Emerging research suggests that shingles vaccination may be associated with a lower risk of dementia.^{25,26}

- **Supporting life-course immunisation:** Shingles vaccination complements other recommended vaccines for adults, contributing to broader healthy ageing strategies and prevention of vaccine-preventable diseases throughout life.¹³

Recombinant zoster vaccine (RZV) to prevent shingles

Previously, Zostavax® [MSD (Pty) Ltd] was the only HZ vaccine available in South Africa.^{12,27} Zostavax® contained the live-attenuated strain of the HZV and one dose of the vaccine was approximately 50% effective at preventing shingles, and almost 67% effective at preventing PHN.^{12,27} However, this vaccine is no longer in production and has now been replaced by Shingrix® [GlaxoSmithKline South Africa (Pty) Ltd] which is a RZV.^{12,28} While there are various HZ candidates in clinical development, including RNA-based and adenovirus-vectored technologies, RZV is currently the only widely available shingles vaccine.¹²

Mechanism of action, immunogenicity, efficacy and effectiveness

The RZV uses a recombinant protein approach based on glycoprotein E (gE), the most important glycoprotein on the VZV envelope and a key target for both humoral and cellular immune responses.^{29,30} The gE antigen stimulates the production of neutralising antibodies while simultaneously activating VZV-specific CD4+ T-cells. This dual immune activation is essential for controlling viral reactivation, as cellular immunity plays a particularly important role in maintaining VZV latency.³¹ The RZV incorporates the AS01B adjuvant system which significantly

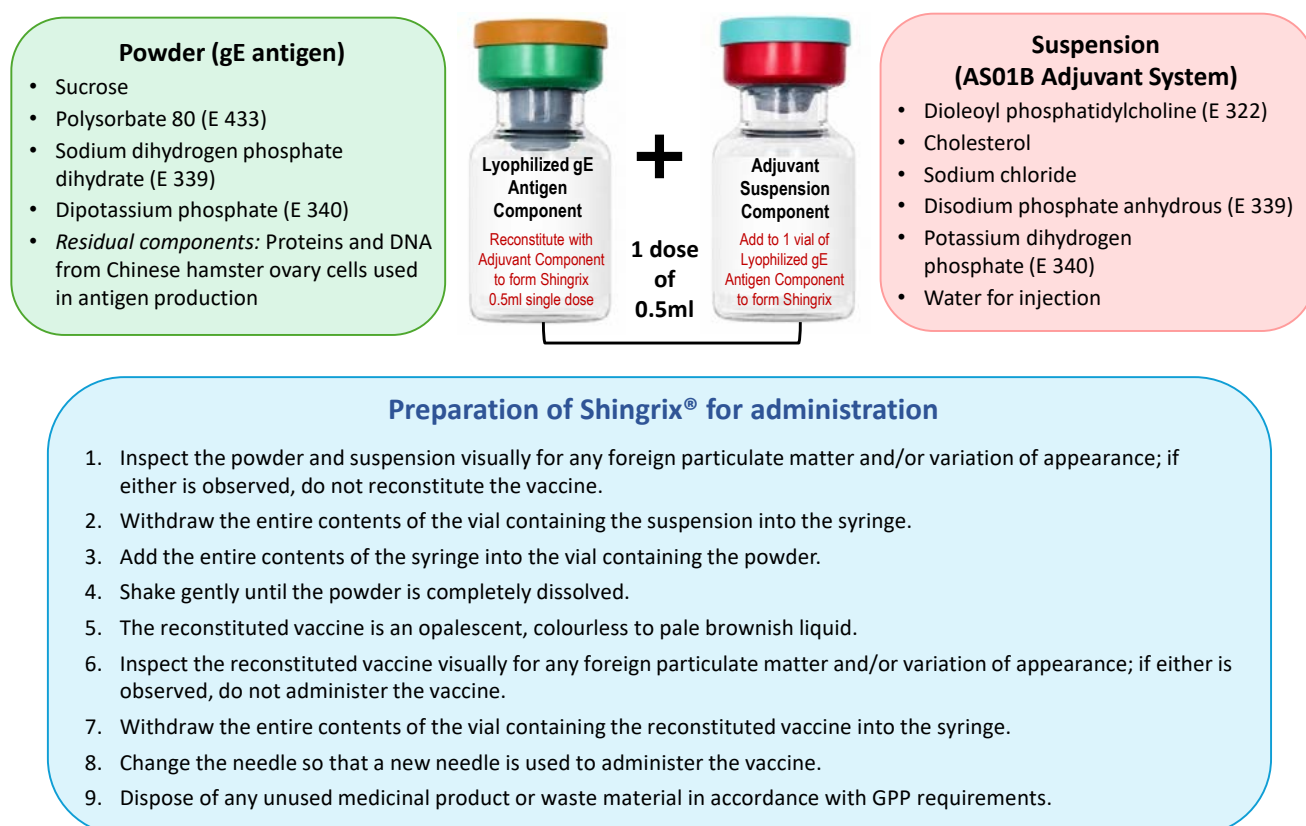


Figure 1: Composition and preparation of Shingrix® for administration²⁸



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- Efficacy demonstrated across patients with underlying chronic medical conditions and immunocompromised adults^{6,7,8,9}
- Durable protection 11 years post vaccination, with an established safety profile²
- Two-dose vaccine administered 2 months apart¹

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PHN: postherpetic neuralgia. **References:** 1. Shingrix approved professional information, July 2025. 2. Strežova A, Díez Domingo J, Cunningham AL, et al. Zoster-049 Study Group. Final analysis of the ZOE-LTFU trial to 11 years post-vaccination: efficacy of the adjuvanted recombinant zoster vaccine against herpes zoster and related complications. *EClinicalMedicine*. 2025;83:103241. 3. Tomlinson C. Why most people in South Africa can't get the shingles vaccine. [cited 2026 Feb 24]; Available from: <https://www.spotlightnsp.co.za/2025/05/27/why-most-people-in-south-africa-cant-get-the-shingles-vaccine/>. 4. Lal H, Cunningham AL, Godeaux O, et al. ZOE-50 Study Group. Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. *N Engl J Med*. 2015;372(22):2087-96. 5. Cunningham AL, Lal H, Kovac M, et al. Efficacy of the Herpes Zoster Subunit Vaccine in Adults 70 Years of Age or Older. *N Engl J Med* 2016;375(11):1019-1032. 6. Costovogel L, Heineman TC, Johnson RW, et al. Medical conditions at enrollment do not impact efficacy and safety of the adjuvanted recombinant zoster vaccine: a pooled post-hoc analysis of two parallel randomized trials. *Human Vaccin Immunother* 2019;15(12):2865-2872. 7. Dagniew AF, Rausch D, Hervé O, et al. Efficacy and serious adverse events profile of the adjuvanted recombinant zoster vaccine in adults with pre-existing potential immune-mediated diseases: a pooled post hoc analysis on two parallel randomized trials. *Rheumatology* 2021;60:1226-1233. 8. Dagniew AF, Ihan O, Lee W-S, et al. Immunogenicity and safety of the adjuvanted recombinant zoster vaccine in adults with haematological malignancies: a phase 3, randomised, clinical trial and post-hoc efficacy analysis. *Lancet Infect Dis* 2019;19(9):988-1000. 9. Batisdas A, de la Serna J, El Idrissi M, et al. Effect of Recombinant Zoster Vaccine on Incidence of Herpes Zoster After Autologous Stem Cell Transplantation A Randomized Clinical Trial. *JAMA* 2019;322(2):123-133.

SHINGRIX ABBREVIATED SAFETY INFORMATION: **Contraindication:** Hypersensitivity to the active substances or to any of the excipients listed in section 6.1. **SPECIAL WARNING & PRECAUTIONS FOR USE:** Postpone vaccination in case of acute severe febrile illness. Do not inject intravascularly, subcutaneously, or intradermally. As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following vaccination. **ADVERSE EVENTS:** Very common – headache, gastrointestinal symptoms, myalgia, injection site reactions, fatigue, chills, fever.

[84] **SHINGRIX** powder for suspension for injection, Herpes zoster vaccine (recombinant, adjuvanted). Each 0.5 mL of the reconstituted vaccine contains: 50 mcg Varicella Zoster Virus (VZV) glycoprotein E antigen. Adjuvanted with AS01 containing: 50 mcg plant extract *Quillaja saponaria* Molina, fraction 21 (QS-21), 50 mcg 3-O-desacetyl-4'-monophosphoryl lipid A (MPL) from *Salmonella Minnesota*. Reg No.: 57/30.2/0735. For full prescribing information refer to the professional information approved by the medicines regulatory authority. **All adverse reactions are to be reported to GlaxoSmithKline by E-mail: aereporting.za@gsk.com or Tel: +27 (0) 10 300 1000.** Additionally, health care providers are to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA website. Trademarks are owned by or licensed to the GSK group of companies. ©2026 GSK group of companies or its licensor. Holder of Certificate of Registration: GlaxoSmithKline South Africa (Pty) Limited, Reg. No.: 1948/030135/07. No 1 Bridgeway Road, Bridgeways Precinct, Century City, Cape Town 7441. Marketed by Adcock Ingram Limited. Co. Reg. No. 1949/034385/06. Private Bag X69, Bryanston, 2021. Customer Care: 0860 ADCOCK/232625. www.adcock.com. 05.20261000005546. PM-ZA-SGX-LBND-2600006 June 2026.



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enhances its immunogenicity. By combining the gE antigen with a potent adjuvant, RZV induces robust and durable humoral and cell-mediated responses. This strengthens immune control of latent VZV, thereby reducing the risk of shingles and its complications, even in older adults affected by immunosenescence.^{31,32}

Clinical trials reported $\geq 90\%$ efficacy of RZV at preventing shingles, and approximately 90% efficacy at preventing PHN, after two doses given 26 months apart.¹² Real-world observational studies have demonstrated vaccine effectiveness of approximately 70% to 85% against shingles. Long-term follow-up studies have further shown that both humoral and cell-mediated immune responses were maintained above pre-vaccination levels for up to 11 years after vaccination, supporting durable protection against shingles.¹²

Vaccine composition and preparation for administration

Shingrix® is supplied as a two-component system requiring reconstitution prior to administration.²⁸ The vial with a brown flip-off cap contains the powder (antigen) and the vial with a blue-green flip-off cap contains the suspension (adjuvant).²⁸ The vaccine contains no preservatives. Figure 1 illustrates the composition of the vaccine and the preparation for administration.²⁸

Storage conditions

Shingrix® must be stored in a refrigerator (+2 °C to +8 °C), in the original package to protect from light and must not be frozen.²⁸ Once reconstituted, the vaccine should be used immediately. If not used immediately, it must be stored in the refrigerator between +2 °C and +8 °C for maximum 6 hours.²⁸

Indications and vaccination of special populations

Shingrix® is indicated for prevention of shingles and PHN in adults aged ≥ 50 years and adults aged ≥ 18 years at increased risk of shingles.²⁸ Shingrix® should be administered in a 2-dose schedule with a minimum interval of 2–6 months between doses.²⁸ The second dose is essential for optimal protection.²⁸ However, according to WHO, the second dose can be administered even if delayed for a year or more.¹² Booster doses are currently not recommended.¹² Specific recommendations for administration include the following:

- **Previous history of varicella (chickenpox) and/or varicella vaccination:** Vaccination may be offered irrespective of previous history. HZV is a reactivated form of VZV which is more common after the age of 50. The disease severity and long-term complications increase with age; thus shingles vaccination is offered from the age of 50 years in many high-income countries.¹²
- **Immunocompromised individuals and those living with HIV:** Shingrix® does not contain any live viruses, hence can be given to immunocompromised patients and those living with HIV from the age of 18 years. This includes individuals with advanced HIV disease, given their increased risk of severe shingles and zoster-related complications. Vaccination will be

most effective once they have received effective antiretroviral therapy for three months.¹² For persons who are or might become immunodeficient or immunosuppressed due to disease or therapy, and who would benefit from a shorter vaccination schedule, the second dose can be administered from one month after the initial dose.¹²

- **Previous episode of shingles:** Because the HZV reactivates, RZV is recommended, with the timing of vaccination determined by individual circumstances. However, the two doses should be administered after all symptoms have completely resolved.¹²
- **Previously vaccinated with the live-attenuated zoster vaccine:** Recommended to be considered for RZV vaccination.¹²
- **Healthcare workers:** RZV is recommended for healthcare workers without evidence of prior VZV infection who care for persons at high risk for varicella.¹²

Vaccine administration and safety considerations

Contraindications

Shingrix® should not be administered to individuals with hypersensitivity to the active substances or to any of the excipients in the vaccine (see Figure 1).²⁸

Precautions for use

Shingrix® vaccine is only intended for prophylactic use and not for treatment of established clinical disease.^{12,28} The following precautions for the use of Shingrix® are recommended:

- **Emergency equipment/kit:** As with all injectable vaccines, appropriate emergency equipment and medical treatment should always be available in case of an anaphylactic event following vaccine administration.²⁸
- **Intramuscular administration only:** Do not administer the vaccine intravascularly or intradermally. Subcutaneous administration is not recommended, as it may lead to an increase in transient local reactions.²⁸
- **Concomitant use:** Shingrix® can be administered concomitantly with unadjuvanted inactivated seasonal influenza vaccine, 23-valent pneumococcal polysaccharide vaccine (PPSV23), pneumococcal conjugate vaccine (PCV), or reduced antigen diphtheria-tetanus-acellular pertussis vaccine (Tdap). Vaccines should be administered at different injection sites. Due to lack of data, concomitant use with other vaccines is not recommended.²⁸
- **Acute severe febrile illness:** Similar to all other vaccines, vaccination should be postponed. However, the presence of a minor infection, such as a cold, should not result in the deferral of vaccination.²⁸
- **Syncope (fainting):** Can occur following, or even before, any vaccination as a psychogenic response to the needle injection. Fainting can be accompanied by neurological reactions e.g. transient visual disturbance, paraesthesia and tonic-clonic limb movements during recovery. Ensure procedures are in place to avoid injury from faints.²⁸

- **Pregnancy:** In the absence of any safety data, the use of Shingrix® should be avoided during pregnancy.²⁸ WHO recommends that RZV may be used in pregnant women when the benefits of vaccination to the pregnant woman outweigh the potential risks e.g. immunocompromised individuals.¹²
- **Breastfeeding:** It is currently unknown whether Shingrix® is excreted in breastmilk.²⁸ WHO recommends the vaccine for lactating women if considered at risk of severe shingles.¹²
- **Thrombocytopenia or any coagulation disorder:** Administer with caution since bleeding may occur following intramuscular administration to these subjects.²⁸
- **Diabetes mellitus:** Shingrix® contains sucrose which may influence the glycaemic control.²⁸
- **Rare hereditary conditions:** People with fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this vaccine.²⁸

Side-effects

Shingrix® is a highly reactogenic vaccine, meaning that it is likely to cause short-term side effects, lasting 2–3 days.^{12,28} The following provides a summary of the side-effect profile of Shingrix®; for detailed information, consult with the professional information of the product:²⁸

- **Very common ($\geq 1/10$):** Systemic (fever, chills, headache, nausea, stomach pain, tiredness, muscle pain) and local (injection site redness, pain and swelling) reactions.²⁸
- **Common ($\geq 1/100$ to $< 1/10$):** Itching around the injection site and generally feeling unwell.²⁸
- **Uncommon ($\geq 1/1\ 000$ to $< 1/100$):** Swollen glands (lymphadenopathy) and joint pain.²⁸
- **Rare ($\geq 1/10\ 000$ to $< 1/1\ 000$):** Allergic reactions may occur

within approximately 15–30 minutes after vaccination. Symptoms include rash and/or hives (swollen welts on skin); and swelling of the face, tongue or throat causing difficulty in swallowing or breathing.²⁸

- **Very rare ($< 1/10\ 000$):** Anaphylaxis is possible after any vaccination.²⁸

One self-controlled study reported a small risk (absolute risk of three cases per million doses) of Guillain-Barré Syndrome (GBS, limb weakness that may lead to partial or full paralysis), observed during the 42 days following vaccination, which is one of the rare complications of shingles itself.²⁸ However, post-marketing surveillance has not confirmed this risk. Thus, RZV is recommended by the WHO, considering that the risk of GBS from shingles itself is much greater than the potential extremely rare risk from the vaccine.¹²

Reporting of adverse events following immunisation (AEFI) is important, as it allows continued monitoring of the benefit/risk balance of the vaccine and detecting rare or unexpected AEFI.²⁸ All suspected AEFI must be reported to SAHPRA through the VigiMobile App (available online at: <https://vigiflow-eforms.who-umc.org/za/aeafi>).

Future directions for life-course vaccination and the role of pharmacists

Population ageing is expected to have major negative impacts on South Africa's health system and economy in the next few decades. According to the latest figures from Statistics South Africa, older persons comprised 7.7% of the total population in 2002.³³ However, this figure has increased to 10.5% in 2025 and is projected to rise sharply to 16.2% by 2050.³³ Although the widespread availability of antiretroviral therapy has markedly improved survival among people living with HIV, the expanding population of ageing

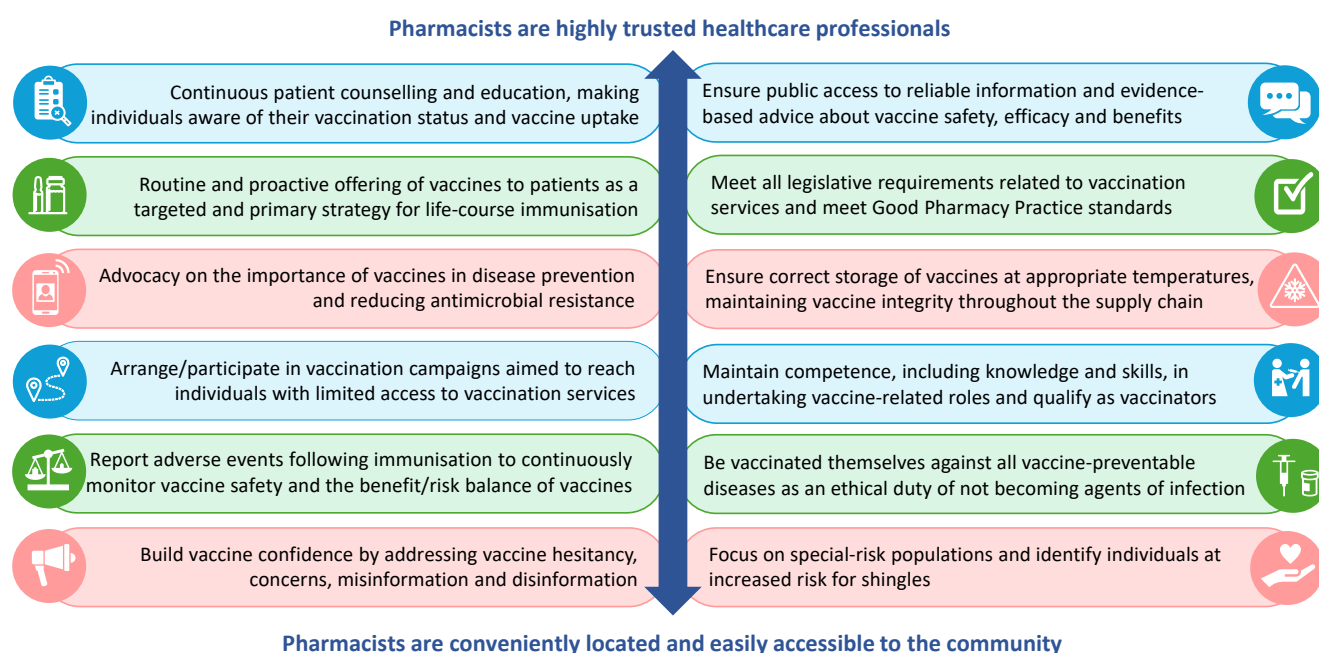


Figure 2: Role of pharmacists in life-course vaccination and enhancing vaccine uptake^{35–38}

individuals with chronic HIV infection, together with increasing life expectancy in the general population, is expected to contribute to a growing burden of shingles in South Africa.^{6,11,13}

Elderly people are at higher risk of vaccine-preventable diseases such as shingles, pneumonia, influenza and COVID-19, which is associated with significant mortality and morbidity, increased hospitalisation and antibiotic use. Vaccination of older adults is therefore an important component of healthy ageing policies, which should be accompanied by strategies to create awareness and demand for vaccination, affordable vaccination services and easy access to these services.¹³ A survey conducted amongst adults ≥ 65 years in public sector community health centres and old age homes across South Africa in 2018, identified very low shingles vaccine uptake with lack of knowledge regarding the availability of the shingles vaccine as a major reason for not receiving shingles vaccination.³⁴ Consequently, strategies aimed at preventing shingles, particularly through vaccination of eligible adults and other high-risk populations, are likely to become increasingly important components of life-course immunisation programmes.^{13,34}

Research has shown that pharmacists are among the most accessible and highly trusted healthcare professionals and are well positioned to support vaccine confidence and uptake.³⁵ Public trust and positive attitudes towards pharmacists are key advantages in achieving the goal of expanding pharmacists' roles as vaccinators.^{36,37} As accessible providers of health information and immunisation services, pharmacists play an important role in addressing vaccine concerns, supporting informed decision-making, and improving vaccine uptake.³⁵⁻³⁸ Figure 2 provides a summary of the role of pharmacists in enhancing shingles vaccine uptake within a life-course immunisation strategy.³⁵⁻³⁸

Potential additional benefits of shingles vaccination

Data on the prevalence of shingles in South Africa are lacking, but a global review published in 2021 reported increasing incidence linked to population ageing, especially in women.³⁹ The incidence of shingles increases markedly with age and immunosuppression, hence older adults and people living with HIV are considered high-risk groups.³⁹ Similarly, limited data are available on the prevalence of dementia in South Africa. However, a modelling study published in 2024, estimated 18% prevalence in South Africa, with dementia prevalence more common as age increases.⁴⁰ Modelling also projected a substantial increase in the prevalence of dementia in South Africa by 2050, with an estimated 1 million people living with dementia in the next few decades.⁴⁰

There is highly credible evidence that vaccination against shingles with either Zostavax® or Shingrix® reduces the risk of dementia. For example, a 2025 systematic review and meta-analysis that included six studies on about 10 million people comparing the unvaccinated to those vaccinated against shingles, found that shingles vaccination reduced the risk of any dementia by 24%, and Alzheimer's disease by 47%.⁴¹ Another study on 329 000 people found that Shingrix® reduced the risk of any dementia by 51%.⁴²

Emerging evidence further suggests that shingles vaccination may confer cardiovascular benefits beyond the prevention of shingles. In a recent cohort analysis of adults ≥ 50 years who received two doses of the RZV, compared with matched unvaccinated individuals, a 72.9% lower risk of HZ ophthalmicus, 83.7% lower risk of PHN, 28% lower risk of hospitalisation for acute myocardial infarction and 42.5% lower risk of hospitalisation for stroke were reported.⁴³ A global systematic review and meta-analysis reported shingles vaccination being associated with a significantly lower risk of stroke and myocardial infarction, indicating the potential cardioprotective effect of shingles vaccination.⁴⁴

Furthermore, there is also a highly credible study that has attempted to explain the biological mechanisms leading to lowered dementia risk, which reported that the biological systems involved in the ageing process, including inflammation, are 'slowed down' by shingles vaccination.⁴⁵

While emerging observational evidence of the additional benefits of shingles vaccination are promising, further research is required to establish causality and determine whether risk reduction of dementia, Alzheimer's disease and cardiovascular events should be considered as additional indications for vaccination.

Conclusion

Shingles remains a significant cause of morbidity, particularly among older adults and immunocompromised individuals, with its burden expected to increase as South Africa's population ages and the prevalence of chronic diseases and HIV remains high. While prompt antiviral therapy and effective pain management are essential to reduce disease severity and complications, vaccination with the RZV has shifted the focus to prevention and is now the most effective strategy for reducing the burden of shingles and PHN.

Pharmacists have a pivotal role to play in identifying individuals at increased risk, promoting vaccine confidence, administering vaccines, providing patient education, supporting early diagnosis, and facilitating timely referral of complicated cases. As accessible and trusted healthcare professionals, pharmacists are well positioned to strengthen life-course immunisation programmes and improve adult vaccine uptake. Expanding pharmacist-led vaccination services and integrating shingles vaccination into routine preventive healthcare will be critical to reducing the clinical and economic burden of shingles and supporting healthy ageing in South Africa.

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Diabetes management

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Abstract

Diabetes mellitus (DM) is a chronic, heterogeneous metabolic disorder characterised by persistent hyperglycaemia resulting from impaired insulin secretion, insulin resistance, or both. The major clinical types include type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), and gestational diabetes (GDM), while less common forms arise from genetic defects, autoimmune processes, metabolic disorders, and secondary causes. Effective management depends on early diagnosis through screening and a combination of pharmacological and non-pharmacological interventions. Non-pharmacological strategies such as diet, physical activity, weight management, and behavioural modification are fundamental to glycaemic control and enhance the effectiveness of pharmacological therapy. Pharmacological management may include insulin and non-insulin agents. Optimised treatment improves glycaemic control, reduces complications, and enhances quality of life. Pharmacists play an expanding role in DM management through screening, patient education, medication optimisation, and ongoing support, contributing to more comprehensive and effective patient care.

Keywords: Diabetes mellitus, disease management, pharmacist role, multifactorial phenotypes, treatment

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Introduction

Diabetes mellitus (DM) is a metabolic disorder characterised by hyperglycaemia resulting from insufficient or ineffective insulin produced by the pancreas. Persistent hyperglycaemia is associated with progressive microvascular and macrovascular complications.¹

DM comprises a heterogeneous group of metabolic disorders with diverse underlying mechanisms, which can be classified into several clinical categories. The most common forms include type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), and gestational DM (GDM). Despite differing underlying mechanisms, all involve dysfunction of pancreatic β -cells resulting in hyperglycaemia.² Beyond these common forms, less common types exist, which are classified according to their underlying aetiology and clinical presentation. These include genetic defects, adipose-related dysfunction, metabolic disorders, autoimmune processes, and secondary mechanisms.

Individuals with DM may present with symptoms of hyperglycaemia, including polyuria, polydipsia, polyphagia, weight loss, and vision disturbances. Patients with T1DM typically present with overt symptoms, whereas those with T2DM may remain asymptomatic, particularly in the early stages.³ Diabetic ketoacidosis (DKA) is a common complication of T1DM and occurs in the setting of insulin deficiency, leading to hyperglycaemia, ketone production and metabolic acidosis. If untreated, DKA may result in life-threatening complications and death.⁴ Patients with T1DM less commonly present with comorbidities, whereas those with T2DM frequently have comorbidities, such as hypertension and dyslipidaemia, which increase the risk of cardiovascular events, including myocardial infarction and stroke.⁵

Screening for T1DM primarily relies on genetic or autoantibody testing.⁶ For T2DM, screening is recommended in overweight adults of any age who present with at least one additional risk

factor. Rescreening should occur at intervals of 3 months to 3 years, and more frequently in individuals with a body-mass index (BMI) ≥ 25 kg/m².⁵ Diagnostic criteria for T2DM include plasma glucose and glycated haemoglobin (HbA1c) thresholds. These include random plasma glucose levels of ≥ 11.1 mmol/L, fasting plasma glucose levels of ≥ 7.0 mmol/L, HbA1c levels of 6.5%, and 2-hour post-load glucose levels of ≥ 11.1 mmol/L, interpreted in conjunction with the characteristic clinical presentation.⁵

Treatment for DM requires a multifaceted approach.⁷ Lifestyle interventions are considered the initial approach in DM. Pharmacologically, metformin is the first-line therapy for T2DM across all age groups,⁸ whereas insulin therapy remains the primary treatment for T1DM.⁹

The expanding role of pharmacists in DM care, encompasses screening, medication optimisation, monitoring, patient education, lifestyle management, adherence support, and preventive care.

Pathophysiology and classification

DM is a chronic and heterogenic metabolic disorder characterised by elevated blood glucose levels (hyperglycaemia) resulting from inadequate insulin secretion, impaired insulin action, or both.¹ Insulin is a peptide hormone secreted by pancreatic β -cells that regulates blood glucose levels by promoting the uptake, utilisation, and storage of glucose.¹ In contrast, glucagon is secreted by pancreatic alpha (α)-cells and increases blood glucose levels by stimulating hepatic glucose production, resulting in an opposing effect to insulin. Both cells are involved in the underlying aetiology of DM, with β -cells being more prominent.¹⁰

DM can be classified into several clinical categories. The most common forms include T1DM, T2DM, and GDM. In addition, less

common forms of DM exist and are typically classified based on specific underlying aetiologies, including genetic, adipose, autoimmune, and secondary mechanisms.

Common forms of diabetes mellitus

Type 1 diabetes mellitus

T1DM is an autoimmune disorder in which the immune system attacks the insulin-producing β -cells of the pancreas.¹¹ This results in an absolute insulin deficiency, requiring lifelong insulin replacement therapy.¹¹ Genetic susceptibility, particularly variations in human leukocyte antigen (HLA)-DR and HLA-DQ genes, influences disease risk, with some alleles increasing susceptibility and others conferring protection, and these patterns vary across populations.¹² T1DM can develop at any age, and the rate of β -cell loss varies between individuals.¹² Autoantibodies directed against insulin and β -cell proteins, including glutamic acid decarboxylate (GAD) 65, insulinoma-associated antigen 2 (IA-2), and zinc transporter 8 (ZnT8), serve as early markers of autoimmunity and may be present long before clinical onset.¹² β -cell destruction is largely mediated by immune and cytokine-driven mechanisms, although the exact pathways in humans are not yet fully understood.¹²

Type 2 diabetes mellitus

T2DM is characterised by two main pathophysiological mechanisms, namely β -cell dysfunction leading to impaired insulin secretion and insulin resistance in peripheral tissues.¹³ It is a complex metabolic disorder, often associated with features of metabolic syndrome and linked to risk factors such as obesity, physical inactivity, and poor dietary habits.¹¹ Inflammation, ectopic lipid accumulation, endoplasmic reticulum and oxidative stress contribute to disease development and progression by promoting insulin resistance and β -cell dysfunction.¹⁴

Insulin resistance, defined as a reduced responsiveness of target tissues to insulin, leads to compensatory hyperinsulinaemia and is strongly associated with metabolic disorders such as obesity, fatty liver disease, and hypertension.¹⁴ Insulin resistance often precedes the onset of T2DM and is therefore considered a major risk factor.¹⁴ In the early stages of insulin resistance, β -cells compensate by increasing insulin secretion to maintain normal blood glucose levels, a response influenced in part by genetic factors.¹⁵ As the disease progresses, β -cells are no longer able to produce sufficient insulin to compensate for rising blood glucose levels, resulting in the development of prediabetes or T2DM.¹³

Gestational diabetes mellitus

GDM is characterised by pancreatic β -cells dysfunction, resulting in an inadequate response to pregnancy-induced insulin resistance.¹⁶ It is typically diagnosed in the second or third trimester of pregnancy in individuals without pre-existing DM.¹⁶ The pathophysiology includes diminished secretion and action of incretin hormones, namely glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which

impairs insulin release.¹⁶ Additionally, pro-inflammatory cytokines such as tumour necrosis factor- α (TNF- α) and interleukin-6 (IL-6) interfere with insulin signalling by disrupting insulin receptor substrate-1 (IRS-1) phosphorylation, thereby impairing glucose uptake.¹⁶

Genetic forms

Monogenic diabetes mellitus

Monogenic DM refers to non-syndromic forms of DM arising from pathogenic variants in a single gene, which are typically inherited following Mendelian patterns.² The two most well-characterised forms of monogenic DM are maturity-onset DM of the young (MODY) and neonatal DM.² Many of the genes underlying these disorders are critical for β -cell development and function.² A prominent feature of monogenic DM is a strong family history, often reflecting an autosomal dominant inheritance pattern across multiple generations. Despite this, affected family members are sometimes misdiagnosed as having T1DM or T2DM.² Neonatal DM most commonly results from loss-of-function variants in the adenosine triphosphate (ATP)-sensitive potassium (K_{ATP}) channel, formed by subunits encoded by potassium inwardly rectifying channel subfamily J member 11 (*KCNJ11*) and ATP-binding cassette subfamily C member 8 (*ABCC8*).¹⁷ Neonatal DM is usually diagnosed within the first six months of life, and if not recognised early, infants may present with severe hyperglycaemia and DKA.¹⁷

Syndromic diabetes mellitus

Syndromic forms of DM are characterised by hyperglycaemia accompanied by a range of atypical clinical features.² Similar to monogenic DM, a positive family history may indicate a genetic cause. However, more severe cases may arise from *de novo* mutations, appearing as sporadic without an apparent familial pattern.² As with MODY, the genes underlying syndromic forms of DM often code for proteins that are essential for the development, function, or survival of β -cells.² Expression of these genes in other tissues may result in multiorgan involvement, including neurological, endocrine, and gastrointestinal manifestations.² An example of syndromic DM is Wolfram syndrome, also known as diabetes insipidus, optic atrophy, and deafness syndrome (DIDMOAD).²

Mitochondrial diabetes mellitus

Mitochondrial DM subtypes arise from mitochondrial dysfunction, often affecting high energy-dependent tissues such as pancreatic β -cells. Inheritance patterns may be maternal, reflecting mitochondrial DNA mutations, or autosomal recessive in the case of nuclear gene mutations.² Mitochondrial disorders show marked clinical and prognostic variability, influenced by factors such as the specific mutation, its level of heteroplasmy, and differences between tissues. The age of onset can vary from early childhood to 40 years or older, although up to 9% of individuals may remain unaffected.¹⁸

Adipose disorder

Lipodystrophic forms of diabetes mellitus management

Lipodystrophic forms of DM are characterised by a loss of body fat, which may be either generalised or localised to a specific area. In this context, insulin resistance is a key driver of hyperglycaemia. Adipose tissue plays a central role in metabolic regulation and insulin sensitivity. Two key adipokines, leptin and adiponectin, regulate metabolism, with leptin promoting satiety and adiponectin enhancing glucose regulation and fatty acid metabolism, thereby contributing to protection against obesity and metabolic syndrome.²

Autoimmune

Latent autoimmune diabetes mellitus in adults

Latent autoimmune DM in adults (LADA) is characterised by the presence of islet autoantibodies without a need for insulin therapy for at least six months after diagnosis in adults. It is often initially misclassified as T2DM. Variation in underlying disease subtypes in LADA may affect both the progression of β -cell dysfunction and the choice of treatment strategies in these patients.²

Ketosis-prone diabetes mellitus

Ketosis-prone DM is defined by the presence of DKA at diagnosis, without the typical features of autoimmune T1DM.² There are four distinct subtypes of ketosis-prone DM based on quantitative measurements of antibody positivity (A+) or negativity (A-) and

presence (β +) or absence (β -) of β -cell functional reserve.¹⁹ Within this classification, A+ β - ketosis-prone DM closely resembles classic autoimmune T1DM, while A- β - ketosis-prone DM presents similarly, however it lacks detectable islet autoantibodies.²

Fulminant diabetes mellitus

Fulminant DM is most commonly reported in individuals from countries in the Far East and is characterised by an abrupt onset, often presenting with DKA despite normal or near-normal HbA1c levels. Although often classified as a subtype of T1DM, patients typically lack islet autoantibodies and have distinct HLA associations. Unlike LADA, β -cell destruction occurs rapidly, often within weeks. This leads to a mismatch between current blood glucose levels and HbA1c values.²

Secondary mechanisms

Severe insulin resistance syndrome

Severe insulin resistance syndromes are primarily driven by defects in insulin signalling, most commonly due to mutations in the insulin receptor gene or disruptions in related metabolic pathways.² These abnormalities impair cellular responsiveness to insulin, leading to compensatory hyperinsulinaemia while glucose regulation progressively deteriorates.²⁰ In some cases, autoimmune mechanisms or alterations in pathways including IGF-1 and fibroblast growth factor 21 (FGF21), further contribute to the underlying pathophysiology.²

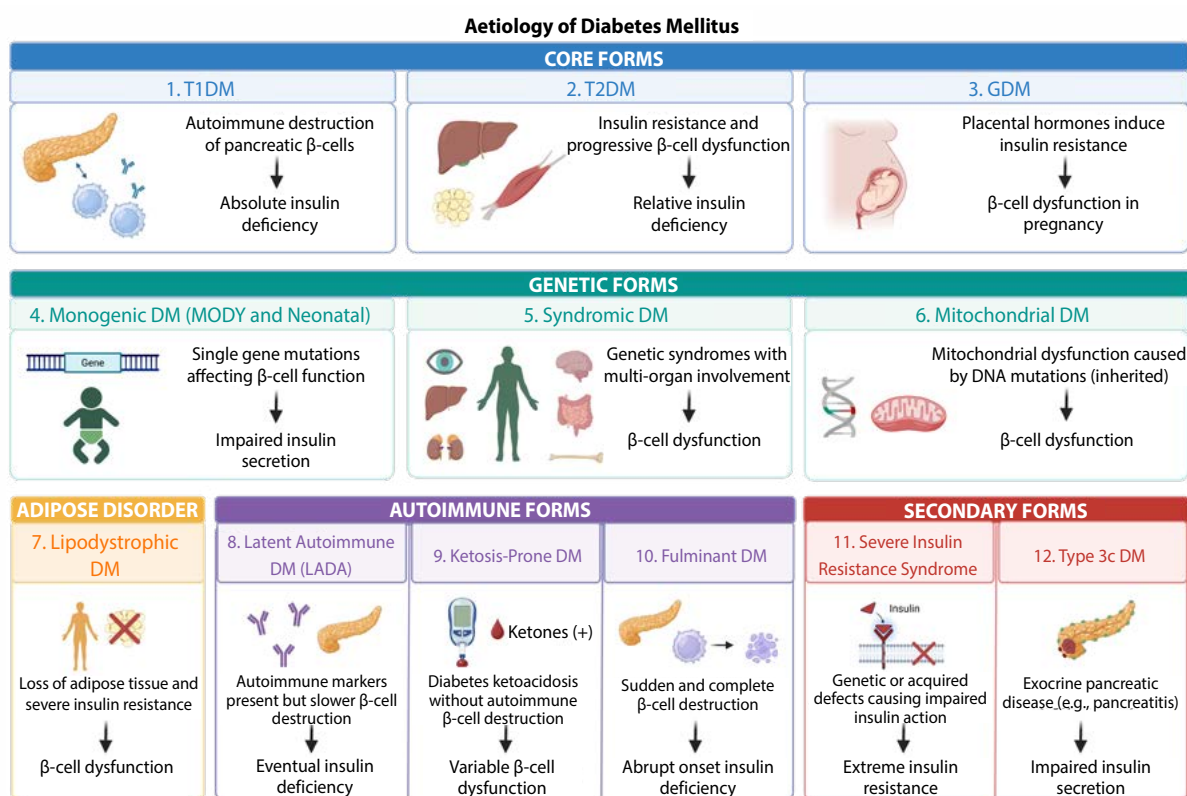


Figure 1: Overview of the aetiology of DM, illustrating core forms (1–3), genetic forms (4–6), adipose disorders (7), autoimmune forms (8–10), and secondary mechanisms (11–12).^{2, 13, 22} Created with BioRender.com

Type 3c diabetes mellitus

Type 3c DM develops through multiple mechanisms resulting from pancreatic damage. Early in the disease process, chronic inflammation or tumour invasion destroys β -cells, leading to reduced insulin secretion. In contrast to T2DM, type 3c DM is characterised by both a quantitative reduction in insulin secretion and qualitative impairment of pancreatic endocrine function, resulting in poor glycaemic control during both hyperglycaemia and hypoglycaemia.²¹

In summary, while the major types share common features of hyperglycaemia, atypical forms highlight the importance of genetic, autoimmune, and secondary factors in disease development. Understanding these distinctions is essential for accurate diagnosis and the implementation of increasingly individualised treatment approaches. Figure 1 outlines the different forms of DM with the underlying aetiology.

Pharmacological and non-pharmacological management

The treatment of DM requires a multifaceted approach that combines behavioural and pharmacological interventions to prevent or delay the progression of long-term complications and maintain quality of life.⁷

T1DM is primarily based on insulin therapy.²³ The different insulin preparations are summarised in Table I. Most patients are initiated on intensive, individualised insulin regimens involving multiple daily injections to mimic endogenous insulin secretion, with once-daily long-acting (basal) insulin combined with rapid-acting (bolus) insulin to cover carbohydrate intake and correct hyperglycaemia.²⁴ In patients with adequate disease understanding and high levels of motivation, a basal-bolus regimen is associated with effective glycaemic control. Although insulin therapy improves glycaemic outcomes and reduces DM-related complications, it is also associated with an increased risk of treatment-induced hypoglycaemia,²⁴ and patients should be educated on adjusting insulin doses according to carbohydrate intake.²⁵ In addition to insulin therapy, dietary modification and physical activity remain important to optimise outcomes, particularly as some patients may be overweight or obese, which may influence insulin requirements and adversely affect metabolic control.²³

T2DM is strongly associated with increased body weight and obesity, often resulting from overnutrition or physical inactivity, and is therefore closely linked to lifestyle factors.²³ Initial management should therefore focus on non-pharmacological interventions, including dietary modification, regular physical activity, weight management, and behavioural support.

Dietary strategies aim to optimise glycaemic control and support weight loss.²³ Structured dietary approaches, such as low-calorie, high-protein diets, improve glucose metabolism and cardiometabolic outcomes, the Mediterranean diet improves

Table I: Insulin preparations for the management of DM^{9,25,28}

Type of insulin	Examples	Onset, peak, duration ^a	Key characteristics and clinical considerations
Rapid-acting insulin analogues	- Insulin glulisine - Insulin lispro - Insulin aspart	Onset: 15–30 minutes Peak: 1–3 hours Duration: 3–5 hours	- Administered immediately before meals (improved convenience vs regular insulin) ↑ Postprandial glucose control ↓ Absorption variability vs regular insulin - Preferred for insulin pump therapy
Short-acting human insulin	Insulin soluble (regular insulin)	Onset: 30–60 minutes Peak: 2–4 hours Duration: up to 8 hours	- Administer 30 minutes before meals - Longer duration of action (dose-dependent) ↑ Absorption variability vs rapid-acting analogues
Intermediate- to long-acting insulin	- Insulin isophane - Insulin zinc	Onset: 1–2 hours Peak: 4–12 hours Duration: 16–35 hours	- Delayed absorption (protamine/zinc complex) - Often requires twice-daily dosing - Commonly combined with short- or rapid-acting insulin - Administered exclusively via subcutaneous route
Long-acting insulin analogues	- Insulin glargine - Insulin detemir - Insulin degludec	Onset: 0.5–1.5 h Peak: No peak ^b Duration: 16–42 h	- Provide basal insulin coverage with minimal/no peak - Reduced variability in absorption - More stable glycaemia control
Premix human insulins (biphasic)	Human premixed insulin: insulin soluble/insulin isophane	Onset: 30–60 minutes Peak: Dual peak Duration: 10–16 hours	- Ready-mixed formulations - Convenient for patients unable to mix insulin - Fixed ratios limit dose flexibility
Premix insulin analogues (biphasic)	- Insulin aspart/insulin aspart protamine - Insulin degludec/insulin aspart - Insulin lispro/insulin lispro protamine	Onset: 5–15 minutes Peak: Dual peak Duration: 10–18 hours	- Can be given within 15 minutes of meals ↑ postprandial glucose control vs human premix

^aThe peak and duration of insulin action may vary depending on factors such as injection site, duration of diabetes, renal function, smoking status, and other patient-specific variables.

^bLong acting insulins are considered "peakless", although minimal peak effects may occur.

glycaemic control, and low-carbohydrate diets improve anthropometric outcomes in patients with T2DM and comorbid obesity.²⁶ It has been shown that resistance exercise contributes to improved muscle function, glycaemic control, and insulin sensitivity, while combined aerobic and resistance training offers greater benefits than single-modality exercise in improving metabolic outcomes.²⁶ Cognitive behavioural therapy has been shown to significantly reduce HbA1c, fasting blood glucose, and diastolic blood pressure.²⁶ In addition, patient education, goal setting, and self-management support play an important

role in promoting adherence and sustaining long-term lifestyle changes.²⁷ In selected patients with obesity, bariatric surgery may be considered and has been shown to result in substantial and sustained weight loss, with potential remission of T2DM.²³

When lifestyle interventions alone are insufficient to achieve glycaemic control, pharmacological therapy should be initiated.^{23,26} Table II summarises the drug classes of glucose-lowering agents targeting different pathophysiological mechanisms. Metformin is the first-line treatment for T2DM across all age groups and is usually prescribed in combination with lifestyle interventions

Table II: Non-insulin pharmacological agents for the management of DM^{7,9,26,28-31}

Drug class	Examples	Mechanism of action	Key clinical considerations
Biguanides	• Metformin	• ↓ hepatic glucose production • ↑ peripheral insulin sensitivity • ↑ GLP-1 secretion	• First-line treatment for T2DM; validated efficacy • Low risk of hypoglycaemia • Promotes weight loss • Risk of GI side effects & vitamin B₁₂ deficiency • Avoid or use with caution in severe renal impairment
Sulphonylureas	• Glimepiride • Gliclazide • Glibenclamide • Glipizide	• ↑ insulin secretion from pancreatic β-cells via closure of K_{ATP}-channels	• Validated efficacy • Risk of hypoglycaemia and weight gain • Use with caution in older adults and in renal impairment
Meglitinides	• Repaglinide • Nateglinide	• ↑ insulin secretion by depolarising pancreatic β-cells (rapid-acting, short duration of action)	• Useful for postprandial glucose control • Risk of hypoglycaemia and weight gain • Safe in elderly patients and renal impairment
Thiazolidinediones	• Pioglitazone	• ↑ insulin sensitivity via activation of PPAR-γ receptors	• Improves lipid profile (↓ triglycerides, ↑ HDL) • Reduce cardiovascular events • Risk of heart failure, oedema, bone fractures, and weight gain • May improve ovulatory function; consider need for contraception
α-glucosidase inhibitors	• Acarbose	• Inhibit intestinal α-glucosidase enzymes • ↓ carbohydrate digestion • ↓ postprandial glucose absorption	• Low risk of hypoglycaemia • Risk for GI side effects • Avoid in renal impairment
GLP-1 receptor agonists	• Exenatide • Semaglutide • Dulaglutide • Liraglutide	• Mimic endogenous GLP-1 • ↑ glucose-dependent insulin secretion • ↓ glucagon secretion • Delay gastric emptying • ↑ satiety	• Low risk of hypoglycaemia • Promotes weight loss • Risk of GI side effects (nausea, vomiting, diarrhoea) • Avoid in severe renal impairment
GIP/GLP-1 receptor agonist	• Tirzepatide	• Dual GIP and GLP-1 receptor activation; enhanced incretin effect • ↑ glucose-dependent insulin secretion • ↓ glucagon secretion • Delay gastric emptying • ↑ satiety	• Low risk of hypoglycaemia • Greater glycaemic control compared to GLP-1 receptor agonists • Significant weight loss • Beneficial effects on BP and lipid profile • Risk of GI side effects (high doses)
DPP-4 inhibitors	• Sitagliptin • Saxagliptin • Vildagliptin	• Inhibit DPP-4 activity; ↑ incretin levels • ↑ glucose-dependent insulin secretion • ↓ glucagon secretion	• Weight neutral • Low risk of hypoglycaemia • Well-tolerated • Risk of heart failure • Potential risk of angioedema/urticaria • Dosage adjustment and caution in renal impairment
SGLT2 inhibitors	• Dapagliflozin • Empagliflozin	• Inhibits SGLT2 in renal proximal tubules • ↓ renal glucose reabsorption • ↑ urinary glucose excretion (glucosuria)	• Low risk of hypoglycaemia • Promotes weight loss and reduces BP • Reduced cardiovascular risk • Risk for genitourinary infections and polyuria • May increase LDL cholesterol • Avoid or use with caution in severe renal impairment

T2DM – Type 2 diabetes mellitus, GLP-1 – Glucagon-like peptide-1, ATP – Adenosine triphosphate, PPAR-γ – Peroxisome proliferator-activated receptor gamma, GIP – Glucose-dependent insulinotropic polypeptide, DPP-4 – Dipeptidyl peptidase-4, SGLT2 – Sodium-glucose co-transporter 2, GI – Gastrointestinal, BP – Blood pressure, HDL – High-density lipoprotein, LDL – Low-density lipoprotein, β-cells – Beta cells, K_{ATP} – Potassium adenosine triphosphate

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*Treatment duration of 24 weeks; results measured at Weeks 4, 8, 12, 16, 20 and 24.

BMI, body mass index; FBG, fasting blood glucose; HbA1c, glycated haemoglobin; PPBG, postprandial blood glucose; SA, South Africa; T2DM, type 2 diabetes mellitus

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such as exercise.⁷ If glycaemic control is not achieved, second-line therapy typically includes sulfonylureas or meglitinides, which act as insulin secretagogues. However, these agents are often only effective in the short term.⁸

Insulin therapy may be required when glycaemic targets are not achieved with the aforementioned non-insulin agents, particularly in advanced disease or in the presence of significant hyperglycaemia.⁸ In T2DM patients, insulin is commonly initiated as either a once-daily injection of intermediate- or long-acting insulin with rapid dose titration, or as a combination of short- and intermediate-acting insulin used alongside metformin. However, more complex regimens may be required over time to achieve optimal glycaemic control.²⁵ Treatment may also be individualised with other glucose-lowering agents targeting different pathophysiological mechanisms, based on patient-specific factors which is outlined in Table II.

Gestational DM is primarily managed with physical activity and dietary modifications similar to those used in T2DM. However, adequate carbohydrate intake is required to support foetal development. If glycaemic targets are not achieved, pharmacological therapy should be initiated. Insulin therapy remains the treatment of choice, as it does not cross the placenta and is therefore considered safe for the foetus. In addition, metformin may be used as an oral agent, however, other medications are not recommended due to the potential for adverse foetal outcomes.¹⁶ Atypical forms of DM are managed using precise medicine approaches tailored to the underlying aetiology and clinical presentation, with insulin and oral glucose-lowering agents commonly used, in conjunction with supportive therapies where appropriate.²

Role of the pharmacist

Pharmacists play a multifaceted role in DM care, including screening, patient education, medication optimisation, adherence support, and prevention of complications.

Screening risk identification and referral

The global rise in T2DM is accompanied by a substantial burden of undiagnosed disease, particularly in high-risk individuals (BMI ≥ 25 kg/m²) and adolescents. This highlights the need for systematic screening, early detection, and timely referral to prevent complications.⁵

Pharmacists serve as a primary point of contact within the healthcare system, positioning them ideally for risk identification. Identifying at-risk individuals before the onset of symptoms represents a critical intervention.³² The Pharmacy DM Screening Trial³³ supports a pharmacy-based, multistage screening protocol as an effective strategy to identify high-risk individuals and enable timely referral. Incorporating point-of-care HbA1c testing alongside risk assessment improved case detection, referral accuracy, and cost-effectiveness compared to risk assessment alone.³³

Patient education

DM education is a structured intervention that supports self-monitoring and informed decision-making, essential for both patients with DM and those at high risk.²⁷ DM self-management education builds knowledge and skills for self-care, while DM self-management support provides ongoing assistance to sustain these behaviours.²⁷

Emerging technologies may support DM education, with evidence suggesting that computer- and mobile-based self-management interventions offer modest improvements in metabolic control, particularly in patients with T2DM.³⁴ The sustainability of educational benefits remains a challenge, as initial improvements tend to decline over time, highlighting the importance for ongoing reinforcement through periodic follow-up and reminder systems, such as phone calls, text messages, and Google calendar reminders.³⁵

Effective self-management is further complicated by multiple individual and environmental barriers, including low health literacy, poor motivation, comorbidities, and sociocultural factors.³⁶ Addressing these barriers requires personalised, patient-centred approaches, with individual sessions often proving more effective than group-based interventions. Culturally adapted education has demonstrated improvements in glycaemic control and disease knowledge, particularly among minority populations.³⁷ Despite its importance, therapeutic patient education remains underutilised, with less than half of patients accessing such programmes, largely due to cost and organisational constraints.³⁸

Collaborative role

Clinical pharmacist co-management within interdisciplinary teams has consistently demonstrated improvements in glycaemic control, particularly in patients with comorbid cardiovascular disease. A prospective randomised study ($n = 1000$) involving cardiac patients with DM reported that pharmacist involvement reduced HbA1c from 10.2% to 8.5%, compared to a smaller reduction in standard care, alongside significant reductions in fasting blood glucose.³⁹

Similarly, evidence from a randomised controlled trial ($n = 239$) demonstrated that pharmacist co-management significantly improved HbA1c (-1.85% vs -0.94%) and increased adherence to preventative care visits, including ophthalmology and dentistry services, reflecting improved coordination across specialties.⁴⁰ Multidisciplinary DM management programmes incorporating pharmacists, endocrinologists, DM educators, and dietitians have also demonstrated substantial improvements in HbA1c (from 11.79% to 7.88% within 3 months), together with improved lipid profiles and blood pressure control.⁴¹ Further supporting this, systematic review and meta-analysis data indicate that pharmacist-led interventions within primary care teams significantly reduce HbA1c (standardised mean difference -0.67), demonstrating consistent benefits across large populations and diverse healthcare settings.⁴²

Despite these benefits, several limitations may restrict the impact of pharmacist involvement, including unclear role definition within multidisciplinary teams, time constraints in busy community settings, inconsistent referral pathways, and gaps in advanced clinical training.⁴³ These factors may restrict pharmacists' contribution to comprehensive DM care, despite their potential to improve outcomes through collaboration and patient education.

Therefore, addressing these challenges requires system-level strategies to clearly define the pharmacist roles, strengthen care coordination, and support effective integration within multidisciplinary teams.⁴⁴ Finally, cultivating a strong team-based care culture remains essential, as interprofessional collaboration improves patient outcomes and reduces duplication of services.⁴⁵

Medication management and optimisation

Medication management and optimisation are essential components of DM control, ensuring that pharmacotherapy is both effective and safe.⁴⁶ Pharmacists are integral in ensuring appropriate dosing and titration of therapy. Ongoing monitoring of treatment effectiveness is essential and typically involves assessing clinical parameters such as HbA1c and blood glucose levels to evaluate therapeutic response and guide treatment adjustments.⁴⁶ Pharmacists contribute significantly to identifying and managing medication-related problems, including adverse drug reactions, poor adherence, and drug-drug interactions, thereby improving patient safety and treatment outcomes.⁴⁶

Adherence support

Medication adherence remains an ongoing challenge in DM management, with suboptimal adherence associated with poor clinical outcomes and increased healthcare costs.⁴⁷ Pharmacists play an important role in identifying patient-specific barriers to adherence, including medication side effects, regimen complexity, and forgetfulness, which are consistently reported as major contributors to non-adherence in patients with DM.²⁷ Adherence interventions include simplifying medication regimens, as well as implementing support strategies such as reminder systems and patient counselling, which has been shown to reduce treatment burden and improve adherence.⁴⁸ Through targeted identification of barriers and implementation of adherence-support interventions, pharmacists can significantly improve treatment outcomes and support long-term disease management in patients with DM.

Monitoring and follow-up

Ongoing monitoring and follow-up are essential components of effective DM management. Pharmacists are integral in supporting self-monitoring of blood glucose by educating patients on interpretation of results, thereby enabling informed self-management decisions.⁴⁹ Regular assessment of long-term glycaemic control through HbA1c measurement is necessary to evaluate treatment effectiveness and guide therapeutic adjustments.⁴⁹ In addition, comprehensive monitoring should include cardiovascular risk factors such as body weight, blood

pressure, and lipid profiles, given their strong association with DM-related complications.⁴⁹ Pharmacists are also well positioned to identify and manage acute glycaemic events, including hypoglycaemia and hyperglycaemia, through patient education and early intervention, thereby improving safety and clinical outcomes.⁴⁹

Prevention and management of complications

Pharmacists are equipped to promote preventive strategies through patient education and referral, including proper foot care to reduce the risk of ulceration, regular eye examinations for early detection of diabetic retinopathy, and measures to protect renal function to prevent diabetic nephropathy.⁴⁹ Pharmacists are skilled to identify early signs of complications through routine patient interaction and monitoring, enabling timely intervention. Prompt referral to appropriate healthcare professionals is essential when complications are suspected, ensuring early diagnosis and management to prevent disease progression and improve patient outcomes.

Management of comorbidities

Pharmacists have a responsibility in the management of hypertension and dyslipidaemia, both of which significantly contribute to cardiovascular morbidity and mortality in patients with DM.⁴⁹ Optimisation of cardiovascular risk factors, including blood pressure and lipid control, is necessary to reduce the risk of macrovascular complications. In addition, pharmacists play an important role in smoking cessation counselling, which remains a key modifiable risk factor in the prevention of cardiovascular disease and overall disease progression.⁴⁹

Specific education and training

Effective use of insulin and DM-related devices requires structured patient education to ensure safe and optimal therapeutic outcomes. Pharmacists should train patients on the correct insulin injection techniques, including site selection, rotation, and administration methods, to ensure consistent absorption and reduce complications such as lipohypertrophy.⁴⁹ In addition, informing patients on the appropriate storage and handling of insulin is necessary to maintain its stability and effectiveness. Improper storage conditions may compromise insulin potency and lead to suboptimal glycaemic control.⁴⁹ Pharmacists are also well positioned to provide hands-on training in the use of DM monitoring and delivery devices, including glucometers, continuous glucose monitoring systems, and insulin pens. Competency in the use of these devices is essential to support accurate monitoring, informed decision-making, and effective self-management.⁴⁹

Ongoing support and behavioural coaching

Pharmacists should provide ongoing motivation and reinforcement to support long-term adherence to treatment plans and lifestyle modifications. Continuous engagement is key, as initial improvements in self-management behaviours

may decline over time without reinforcement.⁵⁰ In addition, psychosocial factors such as DM-related distress can negatively impact self-management and glycaemic control. Addressing these factors through patient-centred communication and supportive counselling helps maintain engagement and reduce the risk of deterioration in outcomes.⁴⁹ Pharmacists should support patients in maintaining behavioural changes and achieving sustained improvements in clinical outcomes.

Conclusion

DM comprises a heterogeneous group of disorders requiring multifaceted management strategies. A holistic, patient-centred approach is essential to address the diverse aetiologies and clinical presentations. This review highlights that pharmacists play an integral role in optimising DM care through screening, medication management, patient education, and adherence support. These interventions contribute to improved glycaemic control, reduced complications, and enhanced patient self-management. Future directions should therefore focus on formalising the pharmacist's role within collaborative care, expanding access to pharmacist-led interventions, and integrating emerging technologies such as continuous glucose monitoring systems and digital adherence tools.

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Redefining Midlife: Empower her menopause

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Abstract

Women experience menopause symptoms that, in some cases, can be debilitating and have a significant impact on everyday activities. Without appropriate care these symptoms can have severe impacts on women's physical and mental health, workplace participation and personal relationships with overall decline in quality of life (QoL).

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The menopause is not a medical condition or disease; it is a natural transition in a woman's life. Up to 80% of women report vasomotor symptoms (VMS) during the transition from early-to-late perimenopause.² VMS are the most common complaint; they are often accompanied by mood changes, panic attacks and anxiety, memory loss, brain fog, urogenital atrophy, reduced sexual function and libido, sleep disturbances, and joint pains.^{1,2} The low oestrogen levels and other biological changes that occur are also associated with an increased risk of cardiovascular disease, osteoporosis, diabetes, and dementia.¹ However, many women suffer in silence; up to 44% have never discussed menopausal symptoms with a healthcare provider either out of fear from taking hormones, their side-effects, weight gain or because of the HCPs not initiating the conversation.³

Time for change

Menopause Hormone Therapy (MHT) has been shown to be the most effective intervention for relief of menopausal symptoms. It also plays a role in QoL improvement, prevention of coronary heart disease, osteoporosis and fracture risk, and reduction in mortality. This is reflected in the guidelines and recommendations from the local and International Menopause Societies. The decision whether to take MHT, the dose and the duration of its use should be made on an individualised basis after discussing the benefits and risks with each patient. Arbitrary limits should not be placed on the duration of usage of MHT.^{1,5,6} MHT is available mainly as oral or transdermal (patches and gel) preparations, all of which contain oestrogen, either alone or combined with progestogen. The benefits and risks vary by origin of product ('body identical' options being preferred), dosage, route of administration, and timing of initiation.⁷

The overall venous thromboembolism (VTE) risk increases about two-fold in women who take oral oestrogens. There is compelling evidence, from large observational studies and meta-analyses together with laboratory studies, that transdermal MHT does not increase the risk of VTE above that in non-users and is associated with a lower risk than oral oestrogens. The type of progestogen significantly affects VTE risk with micronized progesterone (MP) and dydrogesterone conferring a lower risk compared to that with other synthetic progestogens.^{1,6,8,9}

Guidelines recommend transdermal rather than oral MHT for menopausal women who are at increased risk of VTE, including those with a BMI > 30 kg/m².¹

Large observational studies have shown that transdermal administration of oestradiol is unlikely to increase the risk of stroke above that in non-users and is associated with a lower risk of stroke compared with oral administration of oestradiol. MP has been associated with a lower cardiovascular risk and has a neutral effect on blood pressure compared with synthetic progestogens, which have androgenic activities. Consideration should be given to using micronized progesterone with transdermal oestradiol in women who are at increased risk.^{1,7,11}

Different progestogens have different effects on the risk of breast cancer in menopausal women using MHT. A recent meta-analysis has shown that taking oestrogens combined with MP is not associated with an increased risk of breast cancer for the first 5 years. For women taking MHT for > 5 years, risk of breast cancer was lower when taking MP compared with taking a synthetic progestogen.^{1,10,11}

With the increase in longevity and extensive research in recent decades, there has been a greater understanding of the impact and health implications that menopause has on women's lives. "Healthcare practitioners can, and must, protect the health and lives of mid-life women by increasing awareness of the symptoms of menopause, providing healthcare options, namely menopausal hormone therapy, and promoting healthy lifestyle changes. Modifications made before or during the menopausal transition have the most significant impact, even at an older age."¹²

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Anti-obesity medications for the management of obstructive sleep apnoea

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Abstract

Obstructive sleep apnoea (OSA) is a common sleep disorder for which obesity is a major modifiable risk factor that can drive both its onset and chronicity. Accordingly, weight reduction should be a key component of management in individuals with co-existing obesity and OSA. Anti-obesity medications (AOMs) are one potential approach and have long been investigated for this purpose. This narrative review briefly examines the complex mechanisms linking obesity and OSA and critically appraises AOMs as a treatment strategy for individuals with OSA, focusing on agents evaluated for their effects on OSA related outcomes. In this regard, the GIP/GLP-1 receptor agonist, tirzepatide, has shown particular promise in the SURMOUNT-OSA trials, which reported significant reductions in both the apnoea-hypopnoea index and body weight. Other agents, including the GLP-1 receptor agonist liraglutide, phentermine/topiramate, and SGLT2 inhibitors, may confer some benefit, although the effects appear more modest. However, not all individuals with obesity have OSA, nor do all with OSA have obesity. Non-obesity risk factors abound, alongside distinct pathophysiological endotypes that arise in the absence of excess adiposity. Weight loss is thus unlikely to be universally effective as a standalone strategy. Furthermore, weight loss interventions, including AOMs, may be limited by cost, accessibility, and the requirement for long-term use or follow-up. As such, while weight management remains an important component of care for individuals with obesity and OSA, treatment should be individualised and evidence informed.

Keywords: obstructive sleep apnoea, obesity, anti-obesity medications, incretin-based therapies, tirzepatide

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Introduction

Obstructive sleep apnoea (OSA) is a common sleep disorder characterised by recurrent episodes of transient partial or complete upper airway collapse (hypopnoea or apnoea) during sleep, with subsequent airflow reductions despite ongoing respiratory effort.¹ These events are quantified using the apnoea-hypopnoea index (AHI), defined as the average number of apnoeas and hypopnoeas per hour of sleep as measured during polysomnography or home sleep apnoea testing.² The AHI is used to classify OSA severity in adults, with values of 5 to < 15 events/hour indicating mild OSA, 15 to < 30 events/hour indicating moderate OSA, and ≥ 30 events/hour indicating severe OSA. Recurrent airway obstruction leads to intermittent hypoxaemia and repeated arousals from sleep, which then becomes fragmented and non-restorative.³ What ensues is a cascade of sympathetic activation, oxidative stress and systemic inflammation, with downstream neurocognitive and cardiometabolic consequences.⁴⁻⁶ OSA is also associated with reduced work productivity and a heightened risk of occupational and motor vehicle accidents.^{7,8} Individuals classically present with loud snoring, witnessed apnoeas, nocturnal choking or gasping, excessive daytime sleepiness, impaired concentration and mood disturbance, although some may be asymptomatic.^{9,10}

Among established risk factors for OSA, namely male sex, genetics, advancing age, menopause and smoking, obesity is still regarded as one of the most important.¹¹⁻¹⁴ Increased adiposity with fat deposition around the upper airway predisposes to airway collapse, while central adiposity and adipose-derived cytokines

exert additional, albeit less direct, effects.¹⁵ Indeed, the relationship between obesity and OSA may be bidirectional. OSA may foster weight gain and metabolic dysfunction, and in doing so, create a cycle that amplifies health risks and complicates management.¹⁶

While continuous positive airway pressure (CPAP) remains the gold standard for OSA treatment, its effectiveness is often limited by suboptimal adherence, meaning there is a need for acceptable alternatives or adjuncts.^{17,18} Weight loss is associated with improvements in OSA severity^{19,20} and is, therefore, viewed as an essential component of management in people living with obesity and OSA as it targets a key modifiable mechanism while simultaneously addressing other obesity-related conditions.² However, achieving and sustaining weight loss via lifestyle intervention is often unsuccessful and bariatric surgery, although more effective, is invasive and not universally indicated or acceptable.²¹ Anti-obesity medications (AOMs) are a promising alternative, especially amid an expanding pipeline of incretin-based therapies.

Several AOMs have been studied as treatment options for OSA, and in 2024, the US Food and Drug Administration (FDA) approved tirzepatide as the first pharmacological agent specifically indicated for OSA management.²² Despite this significant clinical advance, no single therapy suits all individuals and pharmacotherapies are no exception. As such, this review explores the mechanistic links between obesity and OSA, critically appraises the evidence for AOMs in OSA management, and evaluates their therapeutic potential alongside key limitations.

OSA epidemiology

OSA prevalence is rising, in part fuelled by increasing obesity rates and aging populations.^{23,24} Approximately 1 billion people worldwide live with OSA when defined by an AHI ≥ 5 events/hour, a figure that closely parallels the global prevalence of obesity.^{23,25} While OSA is more common in men, it also frequently affects women.^{26,27} Proposed explanations for the difference in prevalence include variations in upper airway anatomy, chemosensitivity and body fat distribution.^{15,28,29} Problematically, OSA is often overlooked or underdiagnosed in women as they are more likely to present with atypical symptoms such as insomnia, fatigue, depression and morning headaches rather than classic symptoms of snoring and excessive daytime sleepiness.^{27,30} Diagnosis is similarly challenging in older adults, who tend to present with non-specific symptoms that overlap with age-related conditions.³¹

In South Africa, OSA prevalence has been estimated at approximately 23% using an AHI threshold of ≥ 15 events/hour and up to 40% using an AHI ≥ 5 events/hour.²³ Despite these high estimates, actual epidemiological data from Africa remain limited. Evidence from African American cohorts suggests a higher vulnerability to OSA and symptom burden, which might extend to other populations of African ancestry.³²

Besides its clinical consequences, OSA imposes substantial economic and societal costs through direct healthcare expenditure and indirect means such as reduced productivity, absenteeism and an increased risk of occupational and motor vehicle accidents.³³ Although the upfront costs of diagnosis and treatment are significant, effective OSA management is often considered cost-effective or cost-saving by preventing serious long-term sequelae.^{23,34}

The link between OSA and obesity

Obesity, defined as a body mass index (BMI) of ≥ 30 kg/m², is a major modifiable risk factor for OSA and is associated with its presence and severity.^{15,35} In a meta-analysis of community-based cohorts, 74% of individuals with obesity had OSA, as did 60% of those who were overweight ($25 \leq \text{BMI} < 30$), substantially higher than in normal-weight populations.³⁶ Moreover, weight loss is consistently linked with clinically meaningful improvements in OSA severity. BMI reductions of 10%, 20%, and 30% have been associated with approximately 36%, 57%, and 69% decreases in the AHI, respectively.¹⁹ That said, weight gain and weight loss do not necessarily have symmetrical effects on OSA. In another population-based study, a 10% weight gain predicted a 32% increase in AHI, whereas a 10% weight loss predicted a 26% decrease in AHI, suggesting that the “path in” may not mirror the “path out”.³⁷ OSA is also not confined to individuals with obesity. In the aforementioned community-based cohort meta-analysis, only about 32% of adults with OSA had obesity, while about 44% were overweight and 24% were normal or underweight.³⁶ It must be noted that BMI, though widely used in OSA studies, faces scrutiny as both a marker of obesity and a predictor of OSA, and measures

of adipose tissue distribution, such as waist-to-hip ratio and neck circumference, may offer additional discriminatory value.^{35,38–40}

OSA pathogenesis

Understanding how obesity drives OSA requires an appreciation of its underlying pathogenesis, which is complex and involves interactions between anatomical and physiological factors.⁴¹ During inspiration, ventilatory pump muscles generate negative intrathoracic pressure, drawing air through the upper airway and into the lungs. Airflow passes through the pharynx, a collapsible tube surrounded by soft tissues such as the tongue, soft palate, tonsils and pharyngeal fat pads, all enclosed within rigid craniofacial structures.¹⁵ The pharynx stays open during wakefulness due to high neuromuscular tone in upper airway dilator muscles, such as the genioglossus, which surround the pharynx.⁴¹ During sleep, this tone decreases, making the pharynx vulnerable to collapse.^{1,15,41,42} In healthy sleeping individuals, negative pressure fluctuations within the airway and rising CO₂ levels activate reflex mechanisms that augment dilator muscle activity, keeping the airway open.⁴³ However, this compensatory response may be insufficient when there is an imbalance in pharyngeal transmural pressure, which is the difference between intraluminal pressure and surrounding tissue pressure.¹⁵ Such an imbalance can arise when intraluminal pressure becomes more negative during inspiration, particularly in the presence of airway narrowing or obstruction, which amplifies collapsing forces, or when external pressure from surrounding tissues increases.^{16,42} Under these conditions, pharyngeal collapse becomes more likely. When collapse occurs, it results in apnoeas or hypopnoeas, typically terminated by cortical arousals that restore upper airway dilator muscle tone and airflow.¹ Repeated cycles of collapse and arousal fragment sleep and make it difficult to enter sustained restorative sleep stages, thereby contributing to the clinical manifestations of OSA.¹

Four core pathophysiological endotypes have been identified that underpin OSA development and progression.^{1,41,44} The first is increased passive upper airway collapsibility due to structural narrowing, which disrupts transmural pressure. Causes include variations in craniofacial anatomy or excess peripharyngeal soft tissue loading.^{41,45} This is often the predominant mechanism in individuals with obesity. The other endotypes include reduced upper airway dilator muscle responsiveness, unstable ventilatory control (high loop gain) and low arousal threshold.⁴¹ High loop gain refers to an overly sensitive ventilatory control system, in which small fluctuations in CO₂ elicit exaggerated ventilatory responses, leading to instability in respiratory drive and cyclical drops in dilator tone.⁴¹ Meanwhile, a low arousal threshold predisposes individuals to premature and unnecessary arousal in response to respiratory stimuli, before upper airway dilator muscles can be adequately recruited to restore airway patency.⁴¹ The relative contribution of these mechanisms varies between individuals and helps explain differences in OSA susceptibility, presentation and severity, with some traits further exacerbated by chronic OSA itself.⁴⁵

Obesity as a contributor to OSA

Anatomical pathways

In individuals with obesity, excess weight may promote OSA development by inducing anatomical changes that predispose the upper airway to collapse during sleep, primarily through adipose tissue deposition around the pharynx or torso.^{41,45} Fat accumulation within peripharyngeal structures, particularly the tongue, can narrow the upper airway, alter transmural pressure dynamics and thereby increase the risk of collapse.⁴⁶⁻⁴⁸ Corroborating this, a study employing magnetic resonance imaging showed reductions in tongue fat and total lateral wall volumes after weight loss, with tongue fat loss mediating improvements in AHI.⁴⁸ Nonetheless, other factors such as repetitive airway trauma from OSA itself and genetics may also contribute to pharyngeal soft tissue enlargement and similar functional effects independent of adiposity.⁴⁷ For example, chronic snoring and vibratory trauma can result in soft palate inflammation and oedema that may increase upper airway tissue volume.⁴⁸ Furthermore, tongue volume may not necessarily decrease following weight loss.^{15,49}

Apart from local pharyngeal effects, excess abdominal and thoracic adiposity can worsen upper airway collapsibility by reducing lung volume and functional residual capacity (FRC), through mechanical loading.^{1,16,42,45} This diminishes longitudinal caudal traction on the

upper airway, increasing its propensity to collapse. Reduced lung volumes and FRC lower the available oxygen reservoir, which may worsen desaturation during obstructive events and contribute to ventilatory instability.¹

Importantly and consistent with the multifactorial nature of OSA, individuals with and without obesity can still develop OSA due to anatomical factors that are independent of body weight.⁴⁰ Such factors include micrognathia, adenoid hypertrophy, pharyngeal length, or age-, sex- and race-specific factors all of which may increase airway collapsibility.⁵⁰⁻⁵²

Non-anatomical pathways

Obesity may also drive OSA through inflammatory and neurohormonal pathways, although the mechanisms still need to be clearly delineated. Pro-inflammatory cytokines from adipose tissue (adipokines), such as tumour necrosis factor alpha (TNF- α) and interleukin-6 (IL-6), can depress central nervous system activity, potentially impairing ventilatory control and upper airway muscle responsiveness.^{42,45,53-55} Leptin, an adipocyte-derived hormone that regulates energy balance and suppresses appetite, is also thought to be able to modulate ventilatory drive.^{16,56} Its levels rise with increasing fat mass, but leptin resistance in obesity may blunt its central respiratory effects and impair ventilatory control.^{42,56-58}

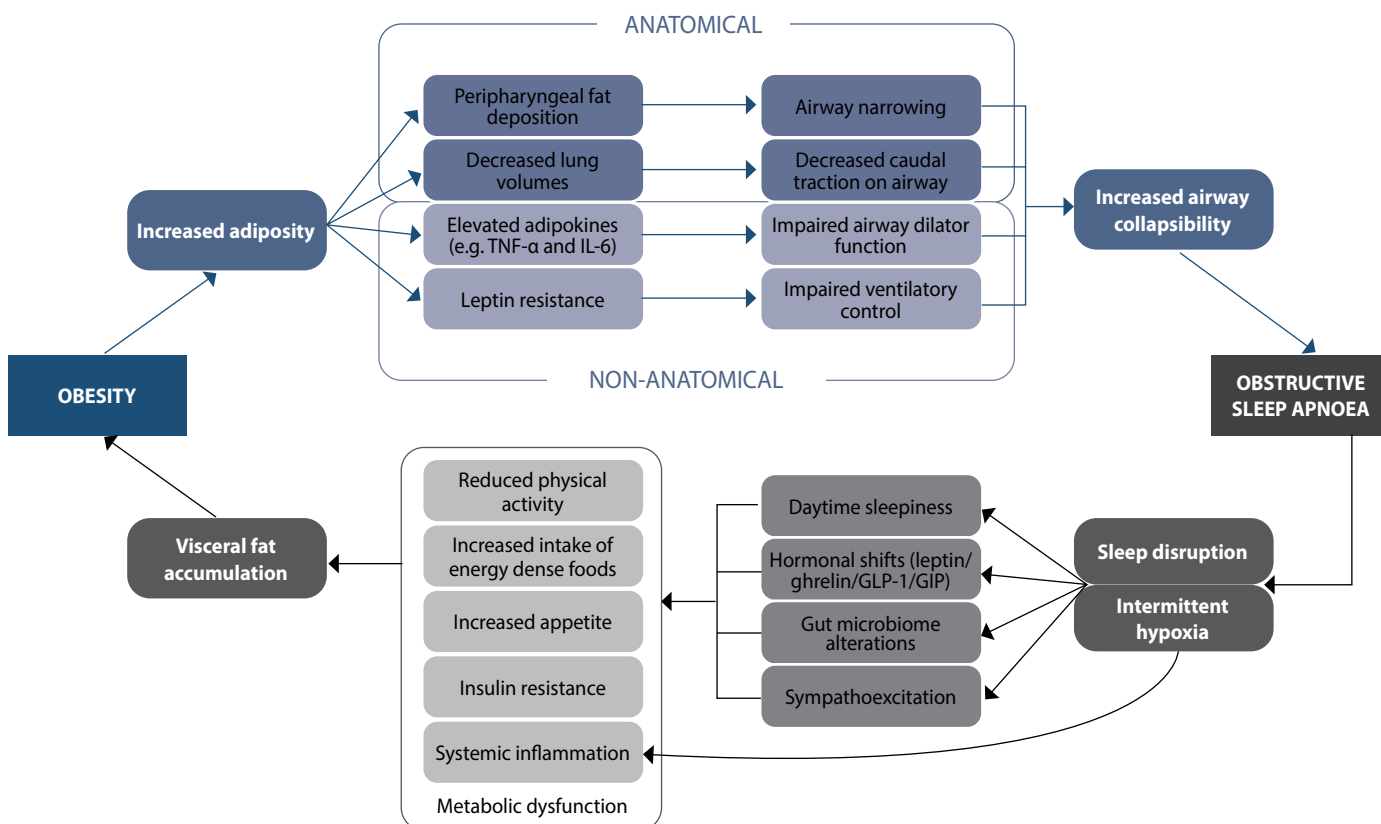


Figure 1: A conceptual mapping of mechanistic pathways linking obesity and obstructive sleep apnoea

The diagram outlines the theoretical framework connecting obesity to airway instability and the subsequent metabolic consequences of OSA. The top section (blue) highlights potential anatomical and non-anatomical contributors to increased airway collapsibility. The bottom section (grey) depicts theoretical metabolic pathways through which OSA may exacerbate visceral fat accumulation and thus obesity, creating a bidirectional loop.

OSA as a contributor to obesity

Weight gain is frequently observed after OSA onset for various reasons, yet underlying mechanisms remain incompletely understood or largely hypothetical.^{16,35} Excessive daytime sleepiness can mediate reduced physical activity and energy expenditure, while sleep fragmentation and intermittent hypoxia may alter levels of key appetite-regulating hormones, leptin and ghrelin, thereby disrupting hunger and satiety signals and increasing the preference for energy dense foods.^{54,59-61} Indeed, individuals with OSA have been shown to exhibit higher levels of leptin than weight-matched controls and reductions in leptin following CPAP therapy suggest that OSA may induce leptin resistance independent of obesity.⁶²⁻⁶⁴ Disrupted sleep patterns in OSA may also alter the secretion of incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which help regulate appetite and insulin release.⁶⁵⁻⁶⁸ Moreover, chronic intermittent hypoxia promotes sympathetic overactivity, both of which independently exacerbate systemic inflammation and glucose dysregulation.⁶¹ Theoretical alterations in the gut microbiome associated with OSA may further exacerbate these disturbances.^{53,69,70} Collectively, these mechanisms may establish a vicious cycle that favours metabolic dysfunction and visceral fat accumulation, which in turn can worsen both obesity and OSA.^{42,59,63,71}

Although CPAP effectively restores airway patency and reduces AHI, it does not reliably promote weight loss. A meta-analysis of 39 randomised controlled trials (RCTs) examining the effects of CPAP on BMI showed small increases in BMI, particularly among individuals using CPAP for less than 5 hours per night.⁷² Proposed mechanisms include reduced work of breathing, loss of hypoxia's anorectic effects, paradoxical alterations in leptin levels that may increase appetite, and shifts in body composition, including fluid retention and increased lean mass.⁶⁴

OSA treatment

CPAP is widely regarded as the mainstay of OSA therapy as it maintains upper airway patency by delivering pressurised air through a nasal or oronasal mask, essentially acting as a pneumatic splint.⁷³ When used consistently, it can reduce daytime sleepiness, enhance quality of life, and mitigate adverse long-term health outcomes, although some controversy exists around the latter.⁷⁴⁻⁷⁷ However, real-world effectiveness is often limited by suboptimal adherence due to factors such as mask discomfort, nasal symptoms, device noise and claustrophobia.^{73,78-80} Alternative or adjunctive options include bilevel positive airway pressure (PAP), mandibular advancement devices, airway surgical interventions, hypoglossal nerve stimulation, medical treatments for nasal obstruction, positional therapy, myofunctional therapy and weight loss, though each has its own indications, efficacy profile and limitations.⁷³

Weight loss as a treatment strategy

Weight loss may be beneficial for some individuals with OSA as it has the potential to target structural contributors. The American

Thoracic Society (ATS) recommends tailored weight loss strategies for adults living with OSA who are overweight or obese, with benefits extending beyond improvements in OSA severity.^{81,82} It advises clinicians to endeavour to provide education on evidence-based weight management and, where appropriate, discuss a stepwise range of options based on patient needs and preferences, including comprehensive lifestyle interventions, pharmacotherapy and bariatric surgery.⁸¹ While lifestyle interventions, such as diet, exercise, or their combination, yield modest reductions in AHI and BMI, sustained clinically meaningful weight loss is challenging with these approaches alone due to compensatory physiological adaptations.^{83,84} For individuals with more severe obesity or refractory weight-related comorbidity, bariatric surgery can achieve substantial weight loss and greater reductions in AHI, with OSA remission rates reported in up to 65% of patients.⁸⁵ However, it is generally reserved for individuals with a BMI $\geq 35\text{ kg/m}^2$, is invasive, carries perioperative risks and requires lifelong nutritional monitoring and follow-up.^{21,69,81} Moreover, improvements in OSA severity are not guaranteed. Anti-obesity pharmacotherapy, on the other hand, offers a more widely applicable and less invasive option. It is recommended for individuals with OSA and a BMI $\geq 27\text{ kg/m}^2$ whose weight has not improved despite a structured lifestyle programme, unless contraindicated.⁸¹ AOMs have long been studied for OSA treatment, starting with the now-discontinued sibutramine.⁸⁶ Therapeutic efficacy in relation to weight loss has improved markedly with newer GLP-1 receptor agonists (GLP-1RAs) and dual GLP-1/GIP agonists. Several systematic reviews and meta-analyses confirm that GLP-1-based therapies produce significant weight loss, which is associated with corresponding reductions in OSA severity, though the number of included studies in these reviews is small and effects may be attenuated in individuals with type 2 diabetes (T2D).⁸⁷⁻⁹⁰ Tirzepatide is the first pharmacological agent approved by the FDA specifically for the treatment of OSA but is yet to be approved by the South African Health Products Regulatory Authority (SAHPRA) for this indication. While certainly meaningful, pharmacotherapy has its drawbacks in OSA management. Rather, these agents expand the pool of available treatment options and may play an important role within a comprehensive, individualised management approach.

Incretin-based therapies

GLP-1 is an incretin hormone released from intestinal L-cells following food intake.⁹¹ It acts via GLP-1 receptors to enhance glucose-dependent insulin secretion, suppress glucagon secretion, slow gastric emptying, and promote satiety, working synergistically with other incretin hormones such as GIP.^{91,92} GLP-1 receptors are found in various tissues, including the central nervous system regions involved in appetite regulation.⁹² Activation is associated with reduced energy intake and subsequent weight loss.^{93,94} GLP-1RAs are medications that mimic endogenous GLP-1 and are primarily used for the treatment of T2D and obesity. Approved agents include semaglutide, liraglutide, dulaglutide, exenatide and tirzepatide, the latter of which is a dual GLP-1/GIP

receptor agonist. Agents specifically approved for weight loss include liraglutide, semaglutide and tirzepatide.

GLP-1 therapies have been investigated for OSA primarily due to their weight-reducing effects, given the strong mechanistic and epidemiological links between obesity and OSA.⁸⁷ However, additional mechanisms have been proposed that are independent of weight loss. GLP-1 receptor activation within hypothalamic centres may enhance respiratory stability and influence sleep-wake regulation, while also modulating breathing through neuroprotective effects and enhanced chemoreceptor responsiveness.⁹⁴ GLP-1RAs also reduce systemic inflammation and associated cytokines such as TNF- α and IL-6, which are implicated in impaired upper airway neuromuscular function and airway collapsibility.^{91,94} Despite their promise, GLP-1RAs have important limitations. Responses to weight loss are not consistently predictable, for reasons not yet fully understood. Landmark clinical trial programmes such as STEP (semaglutide) and SURMOUNT (tirzepatide) showed variability in weight loss, with some participants seeing modest reductions and others profound effects.^{95,96} GLP-1RAs can also have noteworthy side effects and may be poorly tolerated in certain individuals. Furthermore, indefinite use is likely needed to sustain weight loss.⁴⁰

To date, liraglutide and tirzepatide have been the only GLP-1 agents systematically studied in dedicated OSA trials and will be discussed here. Although no trials have specifically examined semaglutide in people with OSA, a small RCT demonstrated reductions in tongue fat volume with semaglutide use in women with obesity and polycystic ovarian syndrome.⁹⁷ Newer agents, such as orforglipron (ATTAIN-OSA)⁹⁸, retratrutide (TRIUMPH)⁹⁹ and maridebart cafraglutide (MARITIME-OSA)¹⁰⁰, are currently in phase 3 trials and are being investigated for their effects on OSA; however, these will not be discussed further as results are not yet available.

Tirzepatide

Tirzepatide is a dual GIP and GLP-1 receptor agonist. In South Africa, it is approved for the treatment of T2D and chronic weight management as an adjunct to health behaviour changes in adults with obesity. It is administered as a once weekly subcutaneous injection, initiated at 2.5 mg and titrated in 2.5 mg increments every 4 weeks, as tolerated, up to a maximum dose of 15 mg weekly, depending on response and tolerability.¹⁰¹ Its weight-reducing effects generally exceed those observed with GLP-1 receptor agonism alone.¹⁰²

The efficacy of tirzepatide in OSA was evaluated in SURMOUNT-OSA, a master protocol comprising two 52-week, phase 3, multicentre, double-blind, randomised, placebo-controlled trials.¹⁰³ Adults with moderate or severe OSA (AHI ≥ 15 events/hour) and obesity (BMI ≥ 30 kg/m², or ≥ 27 kg/m² in Japan) were enrolled. Participants with type 1 or 2 diabetes, recent major weight change, planned bariatric or OSA surgery, central sleep apnoea or major craniofacial abnormalities were excluded. Trial 1 ($n = 234$)

included participants unwilling or unable to use PAP, while Trial 2 ($n = 235$) enrolled individuals established on PAP for at least three months who continued therapy during the study with washout periods at key assessment time points. Participants were assigned to Trial 1 or 2 and then randomised 1:1 to tirzepatide (10 mg or 15 mg) or placebo. All participants received structured lifestyle counselling. Polysomnography was conducted at baseline, week 20 and week 52.

Mean baseline AHI was severe (approximately 52 events/hour in Trial 1 and 50 events/hour in Trial 2), with mean BMI around 39 kg/m² in both trials. At 52 weeks, tirzepatide produced substantial and statistically significant reductions in AHI compared with placebo. In Trial 1, the mean AHI reduction was 25 events/hour with tirzepatide versus 5 events/hour with placebo. In Trial 2, the mean reduction was 29 versus 6 events/hour. These improvements were accompanied by a mean weight loss of approximately 18% (Trial 1) and 20% (Trial 2), and significant reductions in apnoea-specific hypoxic burden, a metric increasingly recognised as a stronger predictor of cardiovascular risk than AHI alone.¹⁰³ In the treatment arm, statistically significant improvements were observed in participant-reported sleep impairment, high-sensitivity C-reactive protein (hsCRP) concentrations and systolic and diastolic blood pressure.

The proportion of participants achieving either resolution of OSA (AHI < 5) or mild disease with minimal symptoms (AHI 5–14 with Epworth Sleepiness Scale (ESS) ≤ 10) at week 52 was 42% versus 16% in Trial 1 and 50% versus 14% in Trial 2 (tirzepatide vs placebo). Thus, roughly half of the participants on tirzepatide did not achieve resolution or mild asymptomatic disease, indicating that treatment with tirzepatide does not guarantee complete remission. Characterisation of the responders would be valuable but was not reported.

The proportion of individuals experiencing any adverse events was broadly similar across arms, although gastrointestinal side effects occurred more frequently with tirzepatide. Gastro-oesophageal reflux was reported in approximately 8% versus 1% of participants (tirzepatide versus placebo) in Trial 1, and 5% versus 0% in Trial 2. This may be clinically relevant as reflux can exacerbate OSA.¹⁰⁴

In summary, the SURMOUNT-OSA trial demonstrated that tirzepatide improves OSA severity and daytime sleepiness, likely mediated through weight loss, with additional potentially favourable effects on metabolic parameters.^{103,105} A key caveat is the absence of direct comparisons between tirzepatide and PAP. Although such comparisons would have been informative and useful, participants in Trial 2 were assessed only after a 7-day washout from PAP. Moreover, PAP adherence was not reported, nor were data provided on PAP tolerability in participants receiving combination treatment. It remains to be elucidated whether combination therapy is feasible in practice and whether tirzepatide may influence PAP tolerability and adherence.¹⁰⁶ The trial design and relatively short 52-week follow-up also precluded assessment of hard cardiovascular outcomes or long-term durability, including

weight and AHI rebound following tirzepatide discontinuation. Women comprised less than one-third of participants and Black individuals approximately 5%, limiting generalisability. Cost and accessibility are also major considerations that will affect real-world implementation and overall benefit. Head-to-head trials, including combination therapy and monotherapy in diverse populations are therefore needed to better evaluate long-term symptom control, cardiometabolic outcomes, adherence and feasibility relative to PAP alone and other established OSA treatments.¹⁰⁵

Liraglutide

Liraglutide is a GLP-1RA approved for the treatment of T2D and chronic weight management in South Africa.¹⁰⁶ It is administered as a once daily subcutaneous injection, initiated at 0.6 mg and titrated weekly in 0.6 mg increments, as tolerated, up to a maximum maintenance dose of 3.0 mg.

The role of liraglutide in OSA was evaluated in the SCALE Sleep Apnoea RCT, a 32-week double-blind, placebo-controlled study.¹⁰⁷ The trial enrolled adults with obesity (BMI ≥ 30 kg/m²) and moderate or severe OSA (AHI ≥ 15 events/hour) who were unwilling or unable to use CPAP. Individuals with type 1 or 2 diabetes or central apnoea were excluded. Participants were randomised to receive liraglutide titrated to 3.0 mg daily ($n = 180$) or placebo ($n = 179$). Both groups received structured lifestyle counselling.

Over 70% of participants were male and 19% were Black or African American. Baseline AHI averaged approximately 49 events/hour and the mean BMI was 39 kg/m². At week 32, reductions in AHI were significantly greater in the liraglutide group than in the placebo group (12 versus 6 events/hour). Most of this improvement occurred within the first 12 weeks, with minimal additional reduction thereafter despite continued weight loss.¹⁰⁷ Mean weight loss at week 32 was also significantly greater with liraglutide than placebo (6% versus 2%), and was accompanied by reductions in BMI, waist circumference and neck circumference.

Treatment assignment independent of weight loss did not significantly influence AHI, suggesting that improvements in OSA severity were primarily mediated by weight reduction.¹⁰⁷ Participants who lost more weight were more likely to show improvement in OSA severity category in both groups. Nevertheless, most participants did not transition to a lower OSA severity category during the study period and only about 5% of those treated with liraglutide achieved OSA resolution (AHI < 5 events/hour), compared with 1% in the placebo arm. Liraglutide also produced significant reductions in other metabolic parameters (HbA1c, fasting plasma glucose and systolic blood pressure) but ESS scores and total sleep time did not differ significantly between treatment groups. Side effects, including gastrointestinal-related, were more common in the liraglutide group.

Smaller studies have explored liraglutide in combination with CPAP therapy. In a RCT of 90 adults with T2D on conventional

hypoglycaemic agents and moderate or severe OSA, combining liraglutide with CPAP (compared with standard of care plus CPAP) resulted in statistically significant but modest reductions in BMI (approximately 2 kg/m²) and AHI, from 31 to 26 events/hour.¹⁰⁸ In another proof-of-concept randomised trial comparing CPAP, liraglutide, and combination therapy, greater mean reductions in AHI were seen in adults using CPAP (alone or in combination) than liraglutide alone (43 to 45 events/hour versus 12 events/hour).¹⁰⁹ The liraglutide-alone group showed the greatest mean weight loss (approximately 6 kg), followed by combination therapy (approximately 4 kg). In contrast, the CPAP-only group showed a small, non-significant weight increase but demonstrated improvements in vascular inflammation, unlike the other treatment arms. CPAP adherence in this group was reportedly excellent. The authors suggested that the more modest weight loss in the combination arm may reflect challenges in concurrently managing both interventions, with CPAP adherence also appearing lower than in the CPAP-only group.¹⁰⁹ Importantly, neither study reported outcomes related to daytime functioning, such as daytime sleepiness.

Across the three trials, liraglutide appeared to reduce OSA severity in individuals with obesity, primarily through weight-loss-mediated mechanisms. However, the magnitude of benefit was generally modest, particularly compared with results seen in SURMOUNT-OSA. Complete remission of OSA was uncommon, and long-term cardiovascular benefits remain unknown. This likely explains why liraglutide lacks specific regulatory approval for OSA treatment, despite its weight loss benefits.

Phentermine/Topiramate

Phentermine/topiramate is a combination pharmacotherapy approved for weight management by the FDA, whereas only phentermine, and not the combination, is registered for the treatment of obesity in South Africa.¹⁰⁶ Phentermine is a sympathomimetic amine that suppresses appetite through central noradrenergic pathways, while topiramate is an anti-epileptic agent with weight-reducing properties likely mediated through appetite suppression and enhanced satiety.¹¹⁰ For individuals with OSA and obesity, the combination therapy may offer theoretical advantages beyond just weight loss and consequent reduction in AHI.¹¹¹ Phentermine's stimulant properties could mitigate excessive daytime sleepiness, while topiramate's modest carbonic anhydrase inhibition, a mechanism shared with acetazolamide, could reduce ventilatory instability (loop gain) and potentially stabilise breathing in susceptible individuals with OSA.¹¹¹

Phentermine/topiramate has been evaluated as a treatment option for OSA in a phase 2, randomised, double-blind, placebo-controlled trial which assessed the safety and efficacy of phentermine 15 mg combined with extended-release topiramate 92 mg in adults with obesity and untreated moderate or severe OSA over 28 weeks.¹¹¹ Enrolled participants ($n = 45$) had a BMI between 30 and 40 kg/m² (mean 35 kg/m²) and were unwilling or unable to comply with PAP therapy. Participants were randomised in a 1:1

ratio to treatment or placebo, and both groups received lifestyle modification counselling. Polysomnography was performed at baseline, week 8, and week 28.

At week 28, the primary endpoint, change in AHI from baseline, favoured phentermine/topiramate over placebo. Treatment resulted in a mean reduction of 32 events/hour (from a baseline of 44 events/hour), compared to a reduction of 17 events/hour in the placebo group (baseline 45 events/hour). Weight loss was also significantly greater with treatment, with a mean reduction of 10% compared with 4% in the placebo group. There was a significant positive correlation between percentage weight loss and reduction in AHI, suggesting that improvements in OSA severity were largely mediated by weight reduction.¹¹¹ In addition, 24% of participants on phentermine/topiramate who had a baseline AHI exceeding 45 events/hour experienced OSA resolution (AHI < 5 events/hour), compared with 0% in the placebo arm. However, there were no significant differences in ESS at week 28 between groups and more participants in the treatment group experienced adverse events.

Despite promising results, the interpretation of this trial is limited by its small sample size and relatively short duration. Moreover, the degree to which reductions in AHI translate into sustained improvements in cardiovascular outcomes or long-term disease modification remains unknown. Phentermine/topiramate also has some misuse potential largely because phentermine is a sympathomimetic stimulant related to amphetamine.¹¹² This further highlights the need for longer-term studies to establish durability and safety in OSA populations.

SGLT2 inhibitors

Sodium-glucose cotransporter 2 (SGLT2) inhibitors block glucose reabsorption in the kidney’s proximal tubule, promoting glycosuria and thereby lowering blood glucose levels.¹¹³ They can also induce modest weight loss, reduce blood pressure, and offer cardiovascular and renal protection in individuals with T2D, heart failure or chronic kidney disease.¹¹⁴ FDA-approved agents include canagliflozin, dapagliflozin, empagliflozin, bexagliflozin and ertugliflozin.¹¹³ SGLT2 inhibitors may also have some benefit for individuals with OSA. Meta-analyses show that SGLT2 inhibitor use is associated with an approximately 63–65% lower risk of developing OSA compared with placebo.^{115–117} Similarly, a post hoc analysis of the EMPA-REG OUTCOME trial found that empagliflozin was associated with a reduced risk of new-onset OSA compared with standard care in individuals with T2D and cardiovascular disease;¹¹⁸ however, analysis limitations include reliance on self-

Table 1: Anti-obesity medications studied for individuals living with obesity and obstructive sleep apnoea

Pharmacologic agent	Mechanism of action: Weight-dependent & proposed independent effects on OSA	Key clinical trial	Follow-up	Mean change in AHI number of events/hr Active vs. Placebo	Percent change in body weight: Active vs. Placebo
Tirzepatide	Weight-dependent: GLP-1 acts on hypothalamic centres to increase satiety and also slows gastric emptying; GIP acts synergistically on central receptors to further augment these effects and enhance weight loss	SURMOUNT-OSA ¹⁰³ Trial 1: PAP-naïve Trial 2: PAP-stable	52 weeks	Trial 1: –25.3 vs. –5.3	Trial 1: –17.7% vs. –1.6%
	Weight-independent: Proposed modulation of breathing and sleep-wake regulation via hypothalamic activation, enhanced chemoreceptor responsiveness, and reduction of systemic inflammation (TNF- α , IL-6) with improved neuromuscular function			Trial 2: –29.3 vs. –5.5	Trial 2: –19.6% vs. –2.3%
Liraglutide	Weight-dependent: Acts on hypothalamic appetite centres to increase satiety and decrease hunger while slowing gastric emptying to prolong fullness Weight-independent: Proposed modulation of breathing and sleep-wake regulation via hypothalamic activation, enhanced chemoreceptor responsiveness, and reduction of systemic inflammation (TNF- α , IL-6) with improved neuromuscular function	SCALE Sleep Apnoea ¹⁰⁷	32 weeks	–12.2 vs. –6.1	–5.7% vs. –1.6%
Phentermine/ Topiramate ER	Weight-dependent: Phentermine suppresses appetite via norepinephrine release; topiramate enhances satiety and reduces cravings Weight-independent: Phentermine may mitigate daytime sleepiness; topiramate’s carbonic anhydrase inhibition may reduce ventilatory instability (loop gain), thereby stabilising breathing	Winslow et al. ¹¹¹	28 weeks	–31.5 vs. –16.6	–10.3% vs. –4.2%
	Weight-dependent: Induces glycosuria to promote caloric loss and reduction in visceral adiposity Weight-independent: Natriuresis and osmotic diuresis may attenuate nocturnal rostral fluid shifts that contribute to airway narrowing; potential reduction in OSA-related sympathetic overactivity				
SGLT2 inhibitors e.g., dapagliflozin, empagliflozin		Small clinical studies ^{120–123} (primarily T2D cohorts)	12 to 24 weeks or retrospective	Approximately –11 to –13 events/hour (No placebo comparator)	Modest absolute loss of approximately –2 to –3 kg off CPAP; +2 kg on CPAP (No placebo comparator)

AHI = apnoea-hypopnoea index; CPAP = continuous positive airway pressure; ER = extended release; GIP = glucose-dependent insulinotropic polypeptide; GLP-1 = glucagon-like peptide-1; hr = hour; IL-6 = interleukin-6; OSA = obstructive sleep apnoea; PAP = positive airway pressure; SGLT2 = sodium-glucose cotransporter-2; TNF- α = tumour necrosis factor- α ; T2D = type 2 diabetes; vs = versus

reported OSA and a lower proportion of participants with BMI > 35 kg/m² in the empagliflozin group.¹¹⁹

Smaller clinical studies provide additional support for a potential role of SGLT2 inhibitors in OSA management. In a 24-week randomised study of 36 participants with newly diagnosed T2D and OSA, participants receiving dapagliflozin in combination with metformin demonstrated significant reductions in BMI (approximately 2 kg/m²) and AHI (approximately 11 events/per hour), along with improved ESS scores compared with those receiving glimepiride plus metformin.¹²⁰

A 24-week prospective single-arm study in Japanese participants with T2D, obesity and sleep-disordered breathing (SDB) showed a statistically significant reduction in the 3% oxygen desaturation index, a parameter used to diagnose and quantify SDB rather than AHI, among individuals with moderate-to-severe SDB receiving dapagliflozin, whereas no improvement was observed in those with mild SDB.¹²¹ Overall ESS scores largely remained unchanged.

A retrospective single-arm study of 18 individuals with T2D and OSA who were unwilling or unable to use CPAP showed that SGLT2 inhibitor therapy (canagliflozin, dapagliflozin, or ipragliflozin) was associated with a reduction in AHI from approximately 32 to 19 events/hour as measured by polysomnography, alongside weight reductions (approximately 3 kg) over a median follow-up of 12 weeks.¹²² The number of individuals with severe OSA (defined by the authors as AHI ≥ 15 events/hour) decreased from 12 to 4. Daytime symptoms were not evaluated.

Another study of individuals with T2D and OSA who were established on an SGLT2 inhibitor (luseogliflozin, dapagliflozin, or empagliflozin) or other oral hypoglycaemic agents and were starting CPAP therapy found AHI improved markedly in both groups after 3 months on CPAP (from 34 to 2 events/hour in the SGLT2 inhibitor group and from 44 to 2 events/hour in the non-SGLT2 inhibitor group).¹²³ Mean body weight and BMI increased in both groups, although the increase reached statistical significance only in those receiving SGLT2 inhibitor therapy. Proposed mechanisms for this weight gain include hyperphagia associated with SGLT2 inhibitor therapy, rebound weight gain after prior weight loss and weight gain associated with CPAP initiation.¹¹⁹

Several mechanisms have also been proposed to explain the potential effects of SGLT2 inhibitors on OSA. Foremost is mild weight loss driven by urinary glucose excretion, accompanied by reductions in visceral adiposity through enhanced lipolysis, which may decrease upper airway fat deposition and reduce airway collapsibility.^{94,119} In addition, SGLT2 inhibitor-induced natriuresis and osmotic diuresis may reduce overnight fluid retention and, in theory, attenuate nocturnal rostral fluid shifts that contribute to upper airway tissue pressure.^{119,124} However, these mechanisms remain largely hypothetical.

Overall, evidence examining the effects of SGLT2 inhibitors in OSA remains limited. Most studies are small, short in duration, and largely restricted to individuals with T2D, with a predominance of male participants. There is also considerable heterogeneity

in OSA assessment and limited reporting of concurrent weight loss interventions. Additionally, the frequent use of concomitant medications may have confounded observed effects.¹¹⁹

Limitations and considerations of weight loss pharmacotherapy

AOMs appear to confer benefit to individuals living with OSA primarily through weight reduction. However, given the complexity of OSA aetiology, excess weight is not invariably causal and weight loss alone will not be effective in all individuals. Responses to these medications are also variable, though predictors of response remain poorly characterised for clinical practice and need to be further studied.

Currently, OSA guidelines position weight loss as an adjunct rather than a standalone therapy.⁸¹ The ATS guidelines provide a practical approach as to how to integrate evidence-based weight loss strategies into care, but these predate the FDA approval of tirzepatide for OSA treatment.⁸¹ As such, there is limited formal guidance on how tirzepatide should be integrated into OSA care pathways. In practice, combination or sequential treatment strategies may be necessary, although optimal approaches, including how tirzepatide might augment other therapies, remain undefined. As with all medications, adverse effects, contraindications and drug interactions must be weighed alongside patient comorbidities and symptoms like daytime sleepiness, which may require more rapid relief.

Given the heterogeneity in the therapeutic effects of weight loss, repeat sleep apnoea testing is likely necessary following implementation of a weight intervention, though the appropriate timing is not well established. The American Academy of Sleep Medicine recommends repeat testing following substantial weight change (10–20%), but this practice is minimally supported by direct evidence from RCTs.¹²⁵ The persistence of OSA improvement after discontinuation of anti-obesity pharmacotherapy is also unknown. Considering the well-documented tendency toward weight regain, theorised to be due to the chronic nature of obesity or underlying neurohormonal imbalances, it is reasonable to assume that OSA severity will likely recur.^{40,126} That being said, CPAP is also likely needed indefinitely, unless the specific underlying endotype(s) are effectively addressed.⁴⁰

In South Africa, access presents an additional and substantial challenge. SAHPRA has not yet approved tirzepatide for the treatment of OSA and, even if approved, the high cost will likely preclude access for the majority. Existing treatment options, including PAP therapy, surgical interventions and even diagnostic testing, are also expensive and largely confined to the private healthcare sector. While approaches to OSA management might be evolving internationally, particularly with rapid advances in AOMs, South Africa faces the more fundamental challenge of establishing local OSA prevalence, developing context-appropriate guidelines and, more urgently, ensuring equitable access to diagnosis and treatment.

Conclusion

Both OSA and obesity are common conditions with significant health and economic consequences. Their apparent bidirectional relationship and pathophysiological links make weight reduction an important component for individuals with overweight or obesity and OSA, as it has the potential to address an underlying precipitant while improving related comorbidities and complications. The growing range of anti-obesity pharmacotherapies may expand the OSA treatment toolkit, which is important given the limitations of other existing options. However, OSA is a heterogeneous disorder and non-obesity-related endotypes may limit the benefit of weight loss in some individuals. Moreover, not all people living with obesity and OSA will respond to weight loss interventions and identifying predictors of response could enable more personalised management. Future trials of AOMs in people with OSA should include diverse and representative populations, including people of African ancestry, to help clarify who may or may not benefit and, simultaneously, improve generalisability. Finally, research focused on affordable, accessible and sustainable OSA treatment strategies should also be prioritised.

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Evolution of InhA inhibitors as antitubercular agents

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Abstract

Tuberculosis caused by *Mycobacterium Tuberculosis*, has been a major scourge to humankind since time immemorial. The cell envelope of Mtb is uniquely complex and contributes significantly to its persistence and drug resistance. The primary factor determining the permeability of Mtb's outer cell membrane is mycolic acid. The enzyme involved in fatty acid synthesis, primarily in mycolic acid biosynthesis is called enoyl acyl carrier protein (ACP) reductase (InhA). Since mycolic acids are essential components of the Mtb cell wall, inhibition of InhA would disrupt their production. Therefore, targeting InhA remains the preferred target for the development of anti-tubercular agents. This review explores various classes of InhA inhibitors, including triclosan, alkyl diphenyl ethers, pyrrolidine carboxamides, arylamides, sulfonamides, pyrrole derivatives, aminoproline scaffolds, acetamide derivatives, thiadiazole derivatives, hydrazone-containing thiadiazoles, imidazopiperidines, triazole derivatives, methylthiazoles, thiourea-based derivatives, tetrahydropyrans, GEQ analogues, and 4-amino-7H-pyrrolo[2,3-d]pyrimidine derivatives. Each class is examined in terms of its mechanism of action, structure activity relationship (SAR), and prospects for overcoming drug resistance.

Keywords: InhA, tuberculosis, MDR-TB, triclosan, MTB cell wall

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Introduction

Studies related to the survival of *Mycobacterium Tuberculosis* (Mtb), the aetiological agent for Tuberculosis (TB) in human hosts and the development of drugs against this pathogen reveal that the organism uses a complex physiology to adapt to the host environment.¹ Thus, a lot of research has been targeted to key enzymes that allow this pathogen to either survive or remain latent within the host.² One enzyme that has gained much research attraction is enoyl acyl carrier protein (ACP) reductase (InhA), the essential target within the fatty acid production pathway of Mtb. Meaning the development of InhA inhibitors in Mtb may be one step closer to finding the cure for this atrocious disease.³

This review explores the biology of Mtb, highlighting its distinctive cell wall construction, which is crucial for its survival and antibiotic resistance. The cell wall's components, including mycolic acids, arabinogalactan, and peptidoglycan, which are essential for Mtb's viability and serve as key targets for drug development. Since InhA is essential in the fatty acid production pathway of Mtb, the review further explores various classes of InhA inhibitors. By looking at their mechanism of action, SAR, and prospects for overcoming drug resistance.

Tuberculosis

According to the World Health Organization (WHO) Global TB Report for 2024, TB is the most common infectious disease, with a fatality rate higher than that of HIV/AIDS,⁴ with 1.09 million deaths among HIV-negative individuals and 161 000 deaths among people living with HIV (WHO, 2024:2, 10). An estimated 1.25 million people died from TB in 2023, almost twice as many as those who died from HIV/AIDS.⁴ Through coughing, sneezing, or singing, an infected person with active pulmonary TB can release droplet

nuclei containing the bacteria into the air, with coughing being the most efficient at generating infectious aerosols, facilitating the spread of the disease.⁵ In the past, patients showed varying consumption, a symbiotic relationship between the microbe and the host in cavitated lesions, and remained symptomatic for decades.⁶ Widespread Mtb transmission is facilitated by this extended infectivity period.⁷

MTB cell wall

Mtb is a metabolically adaptable bacterium that may change its metabolic pathways in response to medications or other stressors, thereby prolonging its survival. Long-chain mycolic acids, highly branched arabinogalactan, and a cross-linked network of peptidoglycan are the three covalently bonded macromolecules that make up the distinctive cell wall of Mtb.⁸ The primary factor determining the permeability of Mtb's outer cell membrane is mycolic acid.⁹ Mycolic acids are long-chain (C60-C90) β -hydroxylated, α -branched fatty acids that connect trehalose to arabinogalactan.¹⁰

TB treatment

The first-line medications used in initial treatment are isoniazid (INH), ethambutol, rifampicin, and pyrazinamide. Streptomycin, fluoroquinolones (ofloxacin, ciprofloxacin), *para*-amino salicylic acid, cycloserine, aminoglycosides, and terizidone are among the second-line medications.^{3,11} In clinical trials, the medications exhibit cure rates of more than 95%, but in actual treatment programmes, they perform far worse.¹² Prolonged treatments with severe side-effects impair patients' ability to complete treatment, which encourages recurrence in patients while also assisting bacteria in developing resistance.¹⁷ The organism that causes multi-drug-resistant tuberculosis (MDR-TB) is resistant to at least

two significant anti-tubercular medications; INH and rifampicin.¹³ Clofazimine is used in combination with amoxicillin, clavulanic acid, thioacetazone, and linezolid to treat MDR-TB.³ Extensively drug-resistant tuberculosis (XDR-TB) is a condition where there is no response to drug therapy. The treatment plan includes drugs such as sutezolid and rifapentine.^{3,14} The difficulty in controlling TB globally is increased by the introduction of *Mtb* strains resistant to both first- and second-line TB medications.¹⁵ Thus, novel anti-tubercular agents with a different mode of action from those currently deployed in clinics are needed.¹⁶

InhA (Enoyl-ACP Reductase)

An enzyme involved in fatty acid synthesis, primarily in mycolic acid biosynthesis, is called enoyl acyl carrier protein (ACP) reductase (InhA).³ It functions by catalysing the reduction of a trans double bond connected to an intermediate's carbonyl group, which is covalently attached to an acyl carrier protein in the FAS-II pathway, thus facilitating the end of mycolic acid elongation and cell lysis.¹⁴ Consequently, mycolic acids are essential components of the mycobacterial cell wall, and inhibition of InhA would disrupt their production.¹⁷ Therefore, InhA remains the preferred target for the development of medication against *Mtb*. Among the reasons that make InhA a distinctive and interesting target for the creation of anti-tubercular medications is that it has a conserved active site, which is not seen in many other *Mtb* targets.³ Additionally, it not only completes the reaction cycle in fatty acid production but also attracts the reversible reaction processing the carbon atom (C₃) of the acyl chain.^{3,18}

Development of InhA inhibitors

InhA inhibitors are primarily categorised as either direct or indirect inhibitors based on the way they function.^{3,19} The compounds that bind to InhA and prevent the formation of mycolic acid are known as indirect inhibitors, and require activation by *M. tuberculosis*'s catalase-peroxidase enzyme (KatG); these are namely drugs such as INH, ethionamide (ETH), and prothionamide (PTH).^{3,20} Direct inhibitors are favoured as novel drugs to combat MDR-TB as they directly inhibit InhA without requiring any prior activation by KatG. Compounds like triclosan (TCN)/diphenyl ethers, pyrrolidine carboxamides, pyrroles, acetamides, thiadiazoles, triazoles, methylthiazoles, hydrazones, and thiourea-based compounds are examples of direct inhibitors.^{3,21} Compounds that are substrate competitive, like the broad-spectrum antibacterial inhibitor triclosan (TCN), have been extensively recognised and do, in fact, target InhA without the activation of KatG.^{15,22}

Triclosan (TCN)

Developed in the 1960s, TCN (8) is a synthetic broad-spectrum antimicrobial agent²³ that has been widely used in various commercial and healthcare products because of its growth inhibitory potential against bacteria, viruses, and fungi. TCN is believed to function as a small hydrophobic molecule that, when diffused into the bacterial cell wall, exerts its antibacterial effects through non-specific disruption of the cell wall structure.^{24,25}

Despite being a potent InhA inhibitor with a sub-micromolar IC₅₀ of 0.2 µM, TCN shows weak antimycobacterial activity, with a minimum inhibitory concentration (MIC) of 64 µM (Figure 1).¹⁵ Additionally, the lipophilicity of TCN is increased by the presence of chlorine atoms in its structure, which lowers its oral bioavailability and limits its potential as an anti-tubercular drug. Compared to INH, TCN is less potent and requires significantly higher concentrations to have a similar therapeutic effect.²⁶

Sullivan and co-workers determined the structure of TCN with InhA, which only contains one TCN molecule in the active site, to comprehend how TCN binds within InhA.²⁷ They overlaid the C16 acyl substrate (C16-NAC) on the InhA-TCN complex to induce the substrate binding loop of InhA to be ordered as well as enhance the affinity of InhA. It was observed that half of the TCN ring A and the chlorine atom on it overlapped with the thioester carbonyl group and the first three carbons of the acyl chain of the C16 substrate when the two structures aligned.²⁷ As a result, the alkyl diphenyl ethers (TCN analogue) were created by removing the lipophilic chlorine atoms on both rings A and B and replacing the former with an alkyl chain of different lengths.²⁷

Alkyl diphenyl ethers

A series of alkyl diphenyl ethers was created using structure-based drug design as strong InhA inhibitors that work against *Mtb* strains that are both sensitive and resistant to INH.

The study utilised TCN, modified its structure by replacing chlorine atoms on the diphenyl ether rings with different alkyl groups (of varying lengths) to enhance binding affinity and antibacterial activity against *Mtb* (Figure 1).²⁷

As the alkyl chain lengthens from one to eight carbons, the compounds' affinity for InhA increases.²⁸ In particular, 5-octyl-2-phenoxyphenol (9) binds to InhA approximately 200 times more strongly than TCN, as indicated by its K_i value of about 1.1 nM.²⁸ However, beyond a certain point, this tendency stops; for example, C14 diphenyl ether (10) has a significantly lower binding affinity with a K_i of 30.3 nM, showing that excessively long alkyl chains may reduce binding due to steric hindrance within the enzyme binding pocket and decreased optimal positioning of the pharmacophore. As a result, longer chains do not necessarily translate into higher affinity.^{22,28}

Furthermore, a series of novel cyclic azole-substituted diphenyl ether derivatives with *ortho*, *meta*, and *para* substitutions with anti-tubercular activity based on the TCN skeleton were reported by Kini and co-workers (11).²⁴ With MIC values ranging from 2.4 to 3.7 µM, the diphenyl ether derivatives bearing cyclic azole substitutions on ring B demonstrated strong activity against the H37Rv strain of *M. tuberculosis*.

Pyrrolidine carboxamides

Based on the work of He and co-workers hybrid molecules based on the pyrrolidine carboxamide scaffold through systematic modification of rings A, B, and C were developed.²⁹⁻³¹ Substitution

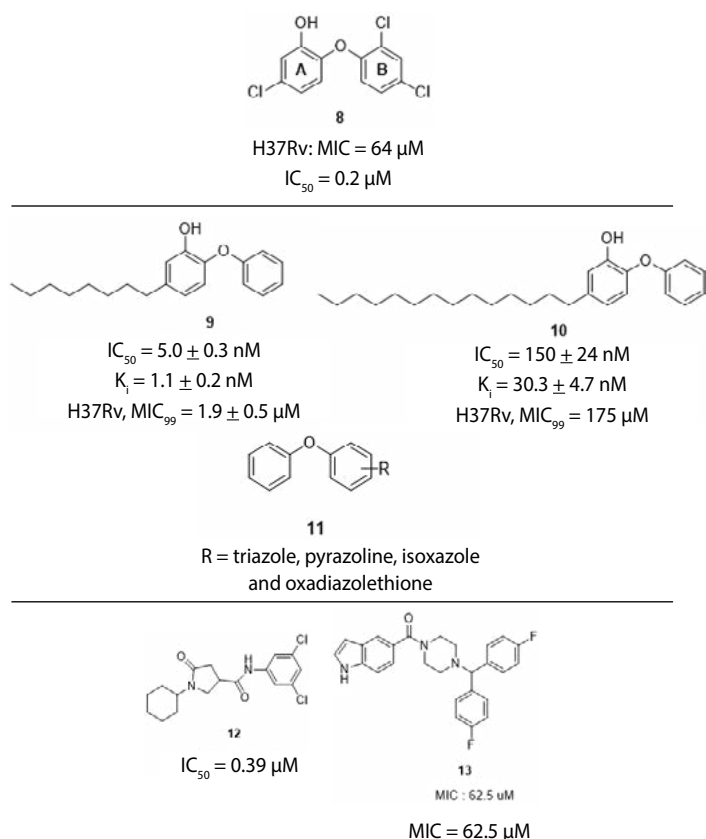


Figure 1: Triclosan, diphenyl ether, pyridine, arylamides derivatives

on phenyl ring A revealed that symmetric 3,5-dichloro substitution significantly improved activity, with compound 12 exhibiting the highest potency (IC_{50} = 0.39 μ M), highlighting the favourable contribution of electron-withdrawing halogens to hydrophobic interactions within the InhA active site.²⁹ Replacement of the pyrrole ring (ring B) led to a marked decrease in activity, indicating its critical role in maintaining the correct orientation and key interactions within the binding pocket.

Modification of the cyclohexyl ring (ring C) showed that ring size strongly influenced activity. Substituted phenyl rings generally reduced potency, while saturated rings of intermediate size, such as cyclohexyl, were optimal. Excessively bulky/too small rings resulted in diminished activity, suggesting a narrow steric tolerance within this region of the binding site.^{22,29}

Arylamides

He and co-workers investigated a series of arylamides, which are characterised by a piperazine or piperidine core (Figure 1).³² The data points to the possibility that molecules with a single electron-withdrawing substituent at the *meta*-position of ring C and at the *para*-position of ring A have good antimycobacterial activity. Furthermore, the presence of dual methyl groups on ring A improves potency; however, bulky substituents at the *para*-position of ring A reduce activity.^{30,32} Activity is increased by substituting fluorine or indole moieties for rings A and C (13).³²

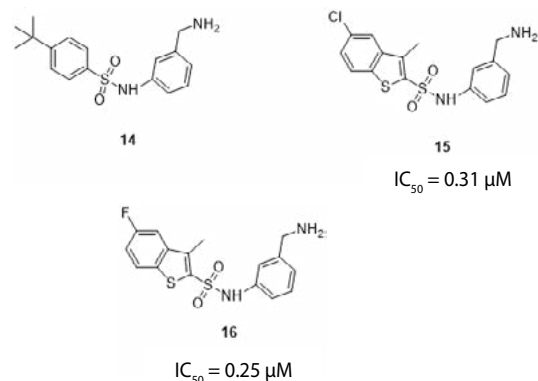


Figure 2: Structures of sulfonamide derivatives

Sulfonamides

A series of sulfonamides (Figure 2) has been investigated as novel InhA inhibitors.³³ Sulfonamide derivatives substituted with an aryl group (14), demonstrated minimal action against the InhA enzyme.³³ Compound 15 increased the InhA inhibition IC_{50} to 0.31 μ M. The efficacy of compound 16 was slightly increased to 0.25 μ M by substituting a 5-fluoro group in place of the 5-chloro group.³³

Pyrrole derivatives

Novel pyrrole derivatives were found to be strong InhA inhibitors, almost as effective as INH.^{3,34} Compounds 17 and 18 exhibited identical anti-tubercular activity, MIC = 0.8 μ g/mL comparable

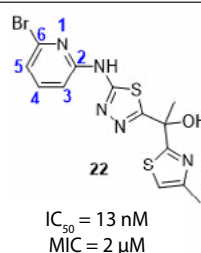
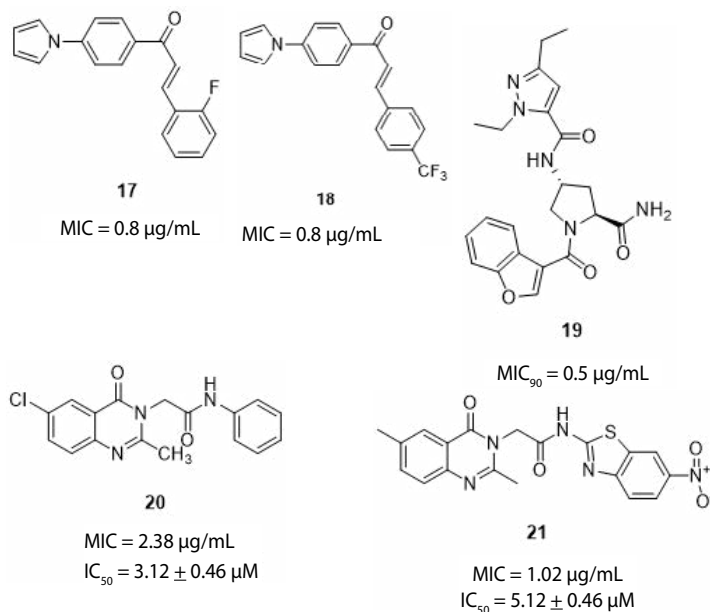


Figure 3: Pyrrolo, aminoproline, thiadiazole, and acetamide derivatives

potency against *M. tuberculosis*. The reported anti-tubercular activity was supported by molecular docking simulations, which showed that the compounds bind to the InhA substrate binding site successfully.³⁴

Aminoproline scaffold

The aminoproline structure was identified as a possible InhA inhibitor. A pyrazole group was added to enhance its effectiveness against the InhA enzyme.³⁵ SAR studies showed that a complete loss of potency occurred when an amine group was added in place of the amide bond. Likewise, N-alkylation of the amide was not tolerated, highlighting that the amide is crucial for enzymatic inhibition.³⁵ Enzymatic activity was similarly impacted by substitution on the pyrazole ring, with certain compounds exhibiting substantial enzyme inhibition but little to no cellular function. Compound 19, balanced lipophilicity, and decreased molecular weight, advanced to *in vivo* testing with an MIC₉₀ of 0.5 µM for the H37Rv Mtb strain.³⁵

Acetamide derivatives

Twenty-eight analogues of 2-(4-oxoquinazolin-3(4H)-yl)acetamide were synthesised and evaluated *in vitro* for Mtb InhA inhibitory activity.³⁶ SARs found that a hydrophobic chloro group at the R1 position improved hydrophobic interactions with the enzyme's active site, resulting in better inhibition (Figure 3).³⁶ Various aryl and heteroaryl groups were investigated at R2 to diversify the compound structures.³⁶ Compound 20 demonstrated the most potent inhibitory activity, with an IC₅₀ of 3.12 µM against InhA. Compound 21, with the 6-nitro-2-benzothiazolyl group at R2, displayed strong inhibitory activity with an IC₅₀ of 5.12 µM. However, docking analysis revealed that while compound 21 formed hydrogen bonds with the ribose hydroxyl group of NAD⁺, it lacked an interaction with Tyr158, which may explain its slightly lower potency.³⁶

Thiadiazole derivatives

Thiadiazole-based competitive InhA inhibitors demonstrated *in vivo* activity against Mtb (Figure 3).³⁷ SAR analysis revealed that the nitrogen atoms present in 2-aminopyridine and 1H-pyrazole-3-amine are critical for activity, likely due to their ability to act as hydrogen bond donors and acceptors thus, adopt favourable protonation states that enhance interactions within the InhA active site. In contrast, pyrimidine rings and substituted phenyl lack appropriately positioned or accessible nitrogen atoms resulting in reduced activity.³⁷ Adding bulkier hydrophobic groups at position 6 of the 2-aminopyridine ring was well-tolerated and maintained good inhibitory activity, with compound 22 being the most potent, IC₅₀ = 13 n and MIC = 2 µM.

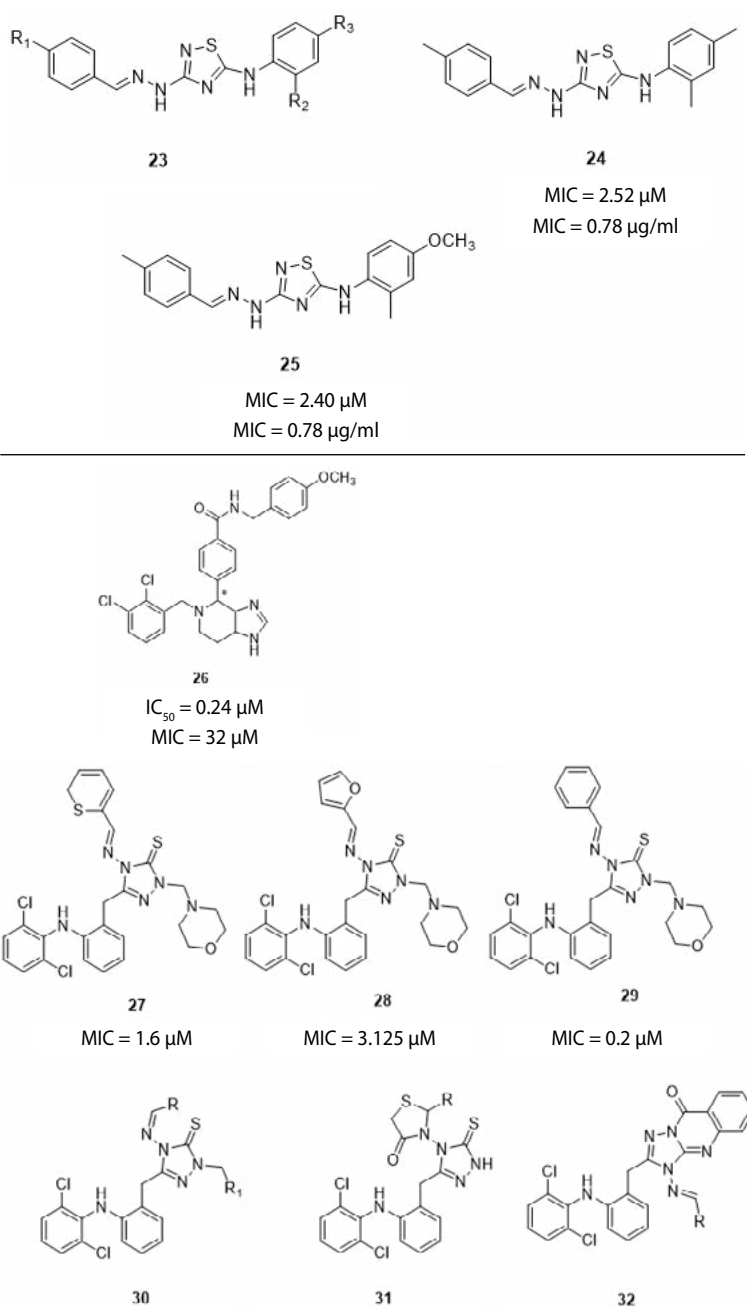


Figure 4: Hydrazone-containing thiazole, imidazopiperidine, and triazole derivatives

Hydrazone-containing thiadiazoles

Compound 23 in Figure 4 presents the general structure of a hydrazone-containing thiadiazoles and the related SARs.³⁸ Adding a methyl group to the benzylidene moiety had little impact on activity. Meanwhile, di-substitution on the N-phenyl ring enhanced antimycobacterial properties.³⁸ Electron-donating groups like methyl (24) and methoxy (25) on the N-phenyl ring significantly enhanced anti-tubercular activity, making compounds 24 and 25 the most active compounds in the series.³⁸

Imidazopiperidines

The study by Wall and co-workers aimed to discover non-covalent InhA inhibitors, seeking new treatments for MDR-TB.³⁹ The unique

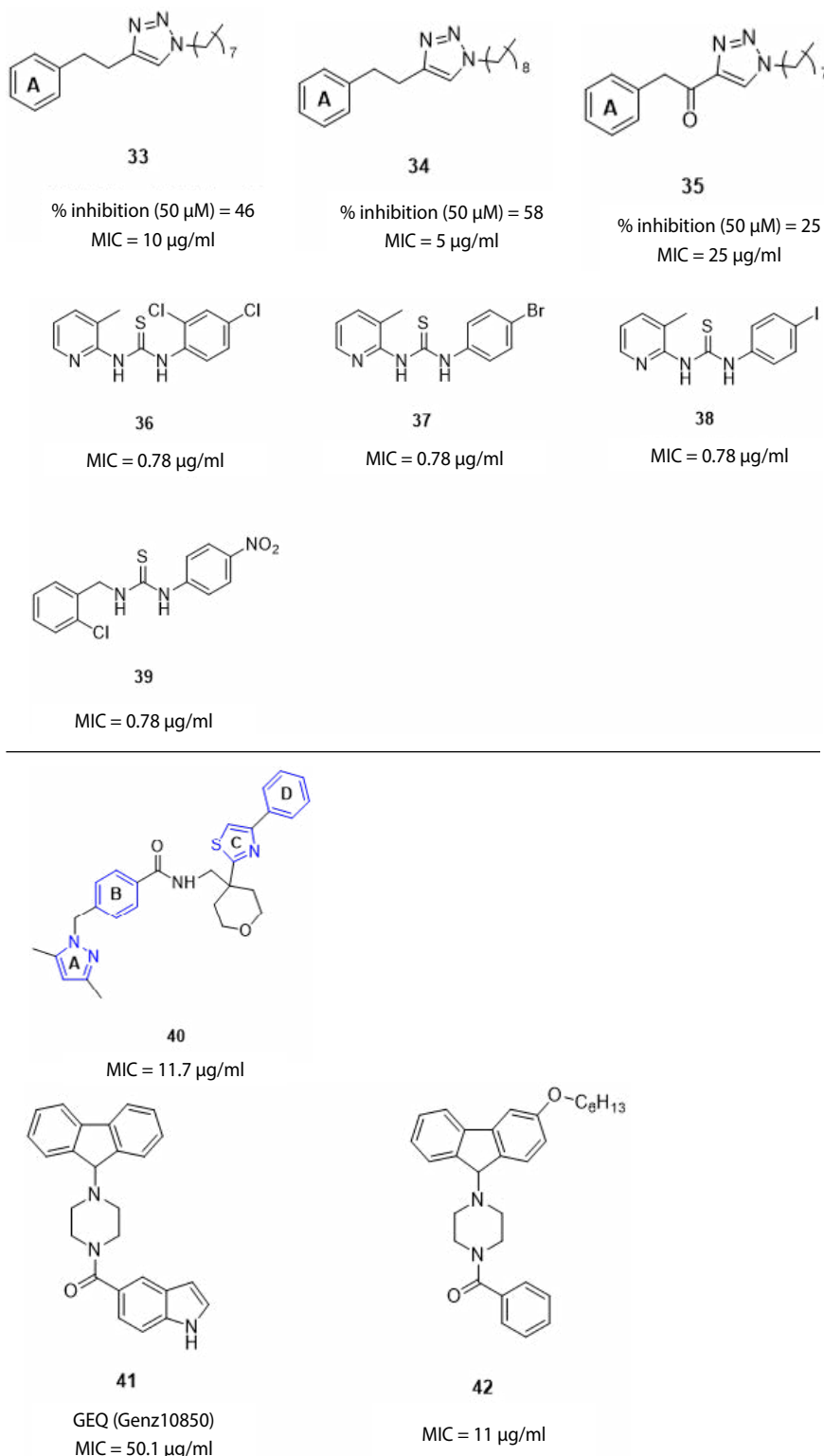


Figure 5: Triazoles, thiourea-based, and GEQ analogues

structure of imidazopiperidine makes it well-suited for solid-phase synthesis, permitting effective optimisation at the carbonyl and piperidine positions based on previous studies.⁴⁰ SAR studies showed that substitutions at R1 and R2 were critical for activity, as shown in Figure 4.³⁹ Compound 26 demonstrated the highest activity in the series, with an IC_{50} of 0.24 μ M.³⁹

Triazole derivatives

Triazoles combined with six-membered rings have been reported to exhibit notable anti-tubercular activity.^{41,42} 3D-QSAR models were developed for SAR analysis.⁴² Compounds 27 and 28 had strong activity with MIC values of 1.6 μ M and 3.125 μ M, respectively. Compound 29 displayed the highest inhibitory activity, with a MIC of 0.2 μ M (Figure 4), likely due to its optimal balance of hydrophobic and polar functionalities, which enables strong interactions within the InhA active site while maintaining favourable membrane permeability, thereby enhancing whole-cell antimycobacterial activity (Figure 4).⁴²

The Mannich base (30) demonstrated better anti-tubercular action than the triazolothiazolidinone (31) and triazoloquinazolinone (32), with morpholine-containing derivatives being more effective than piperidine ones. The oxygen atom of the phenyl ring forms a hydrogen bond with the hydroxyl group of Tyr158, while the phenyl ring's carbon interacts with Leu218.⁴³

1,4-disubstituted-1,2,3-triazoles

Strong anti-tubercular action and moderate InhA inhibition were demonstrated by 1,4-dialkyl-substituted triazole compounds 33 and 34, as well as α -ketotriazole compound 35 (Figure 5).⁴⁴ However, α -ketotriazole derivatives with no chlorine atoms on ring A exhibited little to no inhibition of InhA. Similarly, compounds lacking a carbonyl group failed to exhibit inhibitory activity at a concentration of 10 μ M.⁴⁴ Conversely, compounds with alkyl chains resembling the natural InhA substrate showed increased inhibition, with C8 or C9 alkyl chains showing the highest activity, although longer chains resulted in a lower binding affinity.⁴⁴

Thiourea-based derivatives

To improve the inhibitory capability against the InhA enzyme, structural changes were made to a urea-based ligand by substituting urea with thiourea.^{46,47} Of the synthesised compounds, five compounds demonstrated strong antimycobacterial activity with MIC values of ≤ 1.56 μ g/mL. Among them, compounds 36, 37, 38 (Figure 5), and 39 were particularly notable, each achieving a MIC of 0.78 μ g/mL.⁴⁵ The higher potency of compound 39 can be attributed to subtle structural differences that allow more favourable positioning of the thioketone group within the InhA active site.

Table I: InhA inhibitors table of summary

InhA Inhibitor	IC ₅₀	MIC	Advantages	Limits	Mechanism
Triclosan	0.2 µM	64 µM	Inhibits fatty acid production.	Weak antimycobacterial activity. Less potent than INH.	Antimycobacterial effects through non-specific disruption of the cell wall.
Alkyl diphenyl ethers	150 ± 24 nM-5 ± 0.3 nM	0-175 µM	Strong InhA inhibitors.	Long alkyl chains equal to low binding affinity.	Interfere with fatty acid biosynthesis pathway.
Pyrrolidine carboxamides		0.39-61 c	Direct InhA inhibitors with better bioavailability properties.	Poor whole-cell activity against H37Rv.	Act as a competitive inhibitor of its NADH-binding site.
Arylamides	90 nM		Direct InhA inhibitors.	Low membrane permeability thus, poor whole-cell activity.	Targets type 2 fatty acid biosynthesis pathway.
Sulfonamides		0.07 nM- 162 nm	Overcoming resistance. Effective binding to InhA.	Cross resistance with INH. Poor solubility.	Cell wall inhibition.
Pyrrole		0.8 mg/mL	Strong antibacterial action.		Bind to the InhA substrate site.
Aminoprolines		0.5 µM vs. H37Rv	Potency and balanced lipophilicity.	Challenges in translating enzymic inhibition of effective in vivo outcome studies.	Bind to the InhA substrate site.
Acetamides	3.12 µM		Strong direct inhibitors of InhA.	Low interactions with Tyr 158.	Targets mycolic acid synthesis.
Thiadiazole			Competitive InhA inhibitors. In vivo activity against Mtb.	Limited effective enzyme inhibition.	Form stable interactions within the enzyme's catalytic site (i) and hydrophobic pocket (site ii).
Imidazopiperidines	0.2 µM	32 µM	Non-covalent InhA inhibitor.	Off-target toxicity.	Disrupt mycolic acid biosynthesis.
Triazole		0.2 µM	InhA inhibitor.	Favourable membrane permeability.	Strong interactions within the InhA active site.
Methylthiazoles	0.003 µM	0.19 µM	Direct InhA inhibitor.	Cytochrome P45 inhibition and optimisation challenges.	Binds to InhA in the presence of NAD ⁺ to form a tertiary InhA-NAD inhibitor complex.
Tetrahydropyrans	0.002 µM	11.7 µM	Effective against INH-resistant clinical isolates with mutations in KatG.	Moderate antimycobacterial activity and efficacy.	Interactions with macrophages.
GEQ analogues		4.1-50.1 µM	Promising InhA inhibitors.	Little effect on Mtb due to inadequate cellular permeability.	Binds directly to InhA active site, blocking the binding of the substrate.

Tetrahydropyrans

A high-throughput screening campaign aimed at identifying novel inhibitors of mycobacterial InhA led to the identification of tetrahydropyrans. The study evaluated the influence of the 3,5-dimethyl pyrazole moiety (ring A) on lipophilicity.⁴⁸ Compound 40, which was re-synthesised to ensure sufficient purity and quantity for biological evaluation, demonstrated efficacy against *M. tuberculosis* in macrophages, moderate antimycobacterial activity (MIC = 11.7 µM), and substantial InhA inhibition (IC₅₀ = 0.020 µM).⁴⁸ It was effective against seven INH-resistant clinical isolates with mutations in KatG or upstream of the InhA transcription start site (InhA over-expression).

To interact with NAD, compound 40's pyrazole group (ring A) stacks against its pyridine portion and forms a hydrogen bond with the 2'-hydroxyl group. While the central amide establishes water-bridged interactions with Met98, the methylene linker introduces a kink to guarantee a correct fit in the binding site.

GEQ analogues

It has been determined that the Genz-10850 molecule (GEQ) and its analogues are very promising InhA inhibitors (41) (Figure 5). Although GEQ efficiently inhibits InhA, it has little effect on Mtb, most likely as a result of activation of efflux pumps or inadequate cellular permeability.⁴⁹ Consequently, several fluorene-based derivatives were synthesised to improve InhA inhibition and Mtb growth suppression. The amide group, aryl, fluorene, and piperazine ring were among the structural modifications.⁵⁰

Compound 42, which has an extra hexyloxy group on the fluorene segment, showed the highest inhibition activity against the growth of Mtb and the InhA enzyme.⁵⁰ The anti-tubercular activity of GEQ and its derivatives was increased by efflux pump inhibitors such as reserpine, verapamil, and carbonyl cyanide m-chlorophenyl hydrazone.^{49,50}

Conclusion

Despite treatment progress, TB continues to pose a significant health challenge owing to drug resistance and the constraints of existing medicines. The enzyme InhA is an essential target within the fatty acid production pathway of Mtb.³ InhA inhibitors are categorised into direct and indirect types, with direct inhibitors being preferred for combating MDR-TB. Herein we explore various classes of InhA inhibitors.

Each class is examined in terms of its mechanism of action, SAR, and prospects for overcoming drug resistance. It concludes by emphasising the importance of developing novel direct InhA inhibitors to combat the increasing threat of drug-resistant TB. It highlights the need for further optimisation of these inhibitors to enhance their efficacy, bioavailability, and pharmacokinetics, paving the way for more effective TB treatments.

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Conflict of interest

The authors have no conflict of interest.

Declarations

The writers attest that each of them contributed significantly to this effort. The study was conceived and designed by LL, the first draft was written by AMD, and it was critically revised for intellectual substance by PSD and RMB. The final version was approved by LL, PSD, and RMB. The authors further attest to the work's uniqueness, stating that no data has been falsified or altered and that it has never been published or considered anywhere.

Compliance with ethical guidelines

The authors declare that this submission is in accordance with the principles laid down by the Responsible Research Publication Position Statements as developed at the 2nd World Conference on Research Integrity in Singapore, 2010.

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Organ-on-a-chip: a microfluidic system of next frontier in medicine

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Abstract

Most preliminary drug assessment techniques rely on conventionally simplistic cell cultures and animal models to anticipate pharmacological parameters and toxicological problems. Nevertheless, these conventional methods are laborious and unable to replicate the intricate organic tissue architecture activities. The primary focus of every medication delivery procedure is now the need for an accurate prediction model for determining toxicity and lowering potential risk factors. The creation of organ-on-a-chip (OOC) technology, an interdisciplinary *in vitro* microphysiological platform designed to mimic *in vivo* physiological settings, has attracted increasing scientific attention within the last two years. Researchers throughout the world are increasingly using OOCs for pharmacokinetic/pharmacodynamic (PK/PD) studies, toxicity evaluation, and absorption, distribution, metabolism, and excretion (ADME) profiling. This involves culturing living cells in microfluidic devices that mimic tissue arrangements in living organs. The main goal is to develop specialised disease models and investigate physiological functions in an organ-specific manner. This review focuses on the role of OOCs in toxicological and pharmaceutical applications in place of traditional cell culture models and animal testing. It also examines market share and regulatory issues with the USFDA that need to be addressed if this industry is to live up to its potential to revolutionise the development of drugs and chemical risk assessment in the future.

Keywords: microfluidic, organ-on-a-chip, xenobiotic, pharmacokinetic, pharmacodynamic

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Introduction

The organ-on-chip (OOC) programme was started in 2007 by Donald Ingber, MD, PhD, the founding director of the Wyss Institute, after he looked at an early “lung-on-a-chip” prototype that had microfluidic channels sized to resemble human airway geometry but lacked viable cell integration. Ingber’s group created microfluidic devices with biomimetic molecular scaffolds that could sustain co-cultures of mechanically active human cell types in order to replicate the functional alveolar–capillary interface. The team successfully created the first living human lung-on-a-chip model after thorough device optimisation and iterative prototyping, which was published in *Science* in 2010.¹ The Wyss Institute then created a portfolio of over fifteen physiologically relevant OOC platforms, including kidney, lung, intestinal, and bone-marrow chips, with research funding from the National Institutes of Health (NIH), the US Food and Drug Administration (FDA), and the Defense Advanced Research Projects Agency (DARPA). These systems validated OOC technology as a predictive substitute for traditional preclinical testing models by demonstrating the capacity to replicate human-specific pathophysiological responses and drug-induced effects. The integration of several organ chips into a single, automated microphysiological system known as “body-on-chips” was further made possible by DARPA’s assistance. This platform offers a strong framework for forecasting dynamic drug concentration profiles and therapeutic effects in

conditions relevant to humans by enabling controlled microfluidic coupling of organ models to simulate systemic pharmacokinetics and multi-organ pharmacodynamic interactions.²

Production of an OOC

Microchips, also called microfluidic chips, are tiny devices with one or more micro-channels or micro-tunnels. Their typical dimensions are between 10 and 100 µm. Because surface tension, capillary forces, and laminar flow regimes predominate, fluid behaviour at the microscale is very different from that seen at the macroscale. These phenomena make it possible to precisely manipulate fluids in confined geometries, enabling controlled mixing, pumping, and device designs that are specifically suited to particular experimental needs. For analytical chemistry and experimental biology, microfluidic platforms provide a number of benefits, such as low reagent and sample consumption, accurate flow control, a smaller footprint, less waste production, cost-effectiveness, quick analysis, and the ability to conduct multiplexed assays on a single integrated system.³ OOC devices are designed to cultivate cells in physiologically relevant microenvironments that mimic the structure and function of human organs using microfluidic principles. These devices can replicate tissue-tissue interactions and multi-scale biological processes by offering physiologically appropriate microarchitectures, biochemical gradients, and controlled mechanical cues. Replicating the

dynamic and heterogeneous nature of human physiology is the main goal of OOC technology. The pharmacokinetic and pharmacodynamic evaluation of lead molecules continues to rely heavily on traditional methods, such as animal experiments and two-dimensional (2D) *in vivo* cultures. Nevertheless, these models have intrinsic drawbacks, such as inadequate human-specific response recapitulation, which adds to the high rate of clinical failures for potential treatments. Reliable predictions of drug efficacy and safety in humans are frequently hindered by their incapacity to replicate human physiological conditions. OOCs offer a more sophisticated and physiologically relevant substitute for conventional monolayer cultures and could lessen the need for animal models in drug screening. These microphysiological systems allow for a deeper understanding of human disease mechanisms and therapeutic responses by simulating interactions at the tissue and organ levels. OOC platforms provide better translational relevance and can improve human drug performance prediction because they are populated with primary human cells or stem-cell-derived lineages. This is especially important in therapeutic fields like neuroprotection, where data from animal models frequently don't translate well to clinical results.⁴

Chip production process

The material used to build OOC systems has a significant impact on tissue adhesion and structural organisation. These materials define the microarchitecture of channels and functional features in addition to supporting cellular attachment. The suitability of each material for particular OOC applications is determined by its physicochemical characteristics. One of the most popular materials for OOC fabrication is still polydimethylsiloxane (PDMS), especially in devices made using replica moulding. PDMS replicas are created in this process using a microfabricated master mould, which is usually created using soft lithography. Repetitive silicone–oxygen bonds make up PDMS, a synthetic polymeric elastomer. It is sold commercially as an uncrosslinked silicone prepolymer combined with a curing agent. Complex microstructures can be formed by casting the activated solution over a master mould after it has been mixed.^{5,6} To create a solid, elastomeric chip, the material is then crosslinked using either thermal curing or extended room-temperature incubation. The patterned microarchitecture is revealed when the PDMS layer is removed from the master mould after curing. PDMS components are typically bonded by noncovalent sealing to glass substrates or secondary PDMS layers using plasma oxidation or mechanical pressure. In order to improve manufacturing scalability, these PDMS constructs can either be used directly as functional OOC devices or as moulds for creating devices from secondary materials. PDMS exhibits tunable elasticity, enabling modification of the chip's mechanical properties to closely mimic those of the target tissue, thereby enhancing physiological relevance.^{7,8} Despite these benefits, PDMS has a number of drawbacks. Because of its intrinsic hydrophobicity, bioactive molecules may be absorbed and their effective concentrations during experiments may be drastically changed. Solute concentrations may be further impacted by

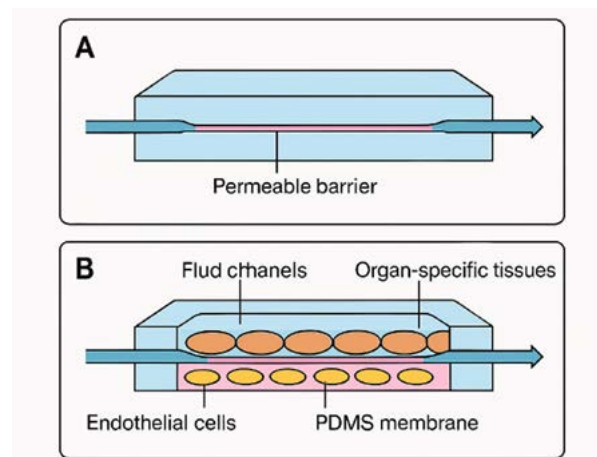


Figure 1: Schematic representation of microfluidic chip. (Created by using BioRender.com)

high gas permeability, which may also hasten water evaporation. Furthermore, PDMS is not biodegradable, which restricts its use in applications that call for transient or biodegradable materials. OOC platforms frequently include extra biomaterials to increase biocompatibility, decrease compound absorption, and improve cell adhesion in order to address these issues.⁹ Figure 1 depicts this fabrication process schematically.

OOC devices can be produced utilising a variety of methods other than the widely utilised PDMS replica moulding technique. In addition to soft lithography, which uses PDMS, polyurethane, or hydrogel-based elastomers to create microchannel structures, thermoplastic manufacturing processes like injection moulding and hot embossing, which employ materials like polymethyl methacrylate (PMMA), polystyrene, polycarbonate, and cyclic olefin polymers, are gaining popularity. By permitting direct development of microchannels without the use of masks, laser micromachining offers quick prototyping possibilities for polymer or glass chips.^{10,11} Photolithography, which uses materials like SU-8 or dry-film resists, enables high-resolution patterning suitable for microscale structures and can be used to fabricate either master moulds or permanent chips; 3D printing technologies, such as stereolithography, digital light processing, and hydrogel-based bioprinting, enable rapid prototyping and the fabrication of complex, customisable microfluidic architectures; and glass micromachining, through wet or dry etching, produces highly stable, chemically inert chips with excellent optical transparency.¹²

Biomaterials used in the production of OOCs

A few essential characteristics must be present in the ideal biomaterial for OOC. The substance must remain intact for a long enough period of time for cells to organise, interact, and draw in more cells. However, it must not persist long enough to obstruct the cell-to-cell communication required for the formation of functional tissue. The ideal scaffolding material will eventually be replaced by the extracellular matrix (ECM) proteins that cells produce. Second, in order to sustain the cells, the biomaterial needs to have sufficient mechanical strength. Third, the porosity

Table I: Several biomaterials used for the preparation of OOC

Organic biomaterials	Features	Limitations	OOC layouts	Ref
Collagen	Biologically compatible, low antigenicity/immunogenicity, degradation by enzymes, cell sticky domains, ability to form into particular geometries, major role in native extracellular matrix, and the ability of cells to rebuild and contract gel matrix. Collagen fibre orientation can be accomplished; cells can enter, Collagen gel can be remodelled and contracted; growth nutrients, proteins, and culture media may be moved across it.	Using chemical crosslinking to improve stability. Collagen-based cell models only hold together for a brief period of time without mechanical assistance.	Cardiovascular, hepatic, skeletal, renal, neuronal networks, tumour spheroids, microvessels, and cancer proliferation	14,15
Chitosan	Biocompatible, biodegradable, structurally similar to glycosaminoglycans, minimal reaction to alien bodies.	Weakness in mechanics and instability.	Vascular.	16
Gelatin	Compatible, biodegradable, less allergenic than collagen, possessing cell attachment sites, and an elastic modulus that is adjustable and medically relevant.	Stability by crosslinking with chemicals.	blood vessels and cardiac muscles.	17
Alginate	Compatible, Biodegradable. When exposed to divalent cations, it immediately gels and may be used as a sacrificial material. The gel also dissolves culture medium.	Unpredictable deterioration. Limited adsorption of proteins. Insufficient cell binding.	Hepatocyte spheroids; cardiac spheroids; liver, tumour, and bone marrow.	18,19
Fibrin	Non-inflammatory, biocompatible, biodegradable, gel-forming at normal temperature due to thrombin's enzymatic synthesis of fibrinogen, and bioadhesive qualities.	Poor mechanical qualities.	Human tissue that is vascularised; musculoskeletal muscle; development of fibrin clots in a lung model.	20
Hyaluronic acid	Naturally occurring ECM component; highly hydrophilic; promotes cell migration and proliferation.	Weak mechanical strength; requires modification for stability.	Used in hydrogel-based OOC systems for tissue engineering and disease modelling.	20
Biomaterials that are synthetic	Adjustable mechanical characteristics. Properties of tunable deterioration. Chemical alteration to include bioactive compounds; reduced variation from batch to batch than biological materials. Hydrolysis breaks down polyesters, making them mouldable.	Absence of cell adhesion ligands before modification; cytotoxic effects from degradation products; and the need to assess the immune response.	Cardiac and hepatic.	21

of the material needs to be suitable. Two crucial elements that influence cell trafficking and material integrity are pore size and scaffold interconnectivity. The two primary categories of biomaterials utilised in organ-on-a-chip systems are artificial biomaterials and organic biomaterials.¹³

Organic biomaterials – Any substance utilised for this purpose that comes from a natural source is considered a natural biomaterial. The ECM constituents, including as Protein peptides collagen, elastin, and hyaluronic acid (HA) are included in these biomaterials. Since natural biomaterials are a part of the native extracellular matrix, their breakdown frequently produces harmless compounds.

Artificial biomaterials – Synthetic biomaterials can help overcome some of the limitations of organically generated biomaterials. One important advantage is that, in comparison to natural biomaterials, synthetic materials are easier to modify in terms of their chemical and physical properties. To meet the requirements of a particular application, these polymers' mechanical properties and rates of degradation can be changed. Numerous variables, such as molecular weight, concentration, and degree of crosslinking, can be changed to adjust these properties. The repeatability

of synthetic biomaterials is another advantageous feature. Compared to naturally generated biomaterials, the processes used to fabricate them may be regulated so that batch-to-batch variability is negligible. The absence of cell adhesion ligands on the surface of synthetic biomaterials is a major drawback. Apart from the above-mentioned characteristics, biomaterials must also be non-cytotoxic and biocompatible with the cells in Table I.

3D printing in OOC technology

With its unmatched design flexibility and capacity to produce intricate, biomimetic microarchitectures, 3D printing has emerged as a revolutionary fabrication technology for OOC systems. Rapid prototyping and precise spatial control made possible by 3D printing, in contrast to conventional lithography-based techniques, allow the creation of curved, branching, and tortuous microchannels that more closely resemble human tissue and vascular structures. Stereolithography, digital light processing, extrusion bioprinting, and two-photon polymerisation are examples of advanced printing modalities that facilitate the use of a variety of materials, including cell-laden hydrogels, elastomers, and photopolymerisable resins. These features improve physiological relevance by enabling the direct integration of biochemical

gradients, extracellular matrix elements, and living cells into the chip environment.²² Even though there are still certain drawbacks, such as limited material biocompatibility, possible cytotoxicity of leftover photoinitiators, and difficulties in obtaining ultra-fine channel dimensions, continuous advancements in bioresins and high-resolution printers continue to increase the usefulness of 3D printing. All things considered, 3D printing greatly advances OOC development by making microphysiological systems highly scalable, functional, and customisable.^{23,24} OOC platforms offer unique benefits that go beyond cellular architecture, even while sophisticated 3D models like organoids and tumour spheroids give better biological complexity than traditional 2D cultures. In particular, OOC systems provide haemodynamic parameters that are not present in static 3D models, such as finely controlled shear stress and continuous dynamic fluid flow. In order to replicate endothelium mechanobiology, nutrition transport, and medication pharmacokinetics under physiologically appropriate flow conditions, these mechanical signals are essential. Additionally, real-time monitoring, multi-organ integration, and controlled co-culture of several cell types inside a single microfluidic system are made possible by OOC platforms; these benefits are intrinsic to the platform and are not limited to any particular organ model.

Current developments in OOC

Using compartmentalised micro-engineering techniques, in recent years, some organ systems have undergone *in vivo* replication. The list of organs for which several microsystem-based methods and approaches have been explained here:^{25,26}

Lung-on-a-chip

One of the most difficult organ systems to study *in vivo* is the pulmonary system, which mediates gas exchange between inhaled air and the bloodstream. Direct manipulation and real-time evaluation of region-specific cellular responses are impeded by the lung's complex three-dimensional geometry, heterogeneous cellular composition, and deep anatomical location. Additionally, the predictive value of conventional *in vivo* models is limited by the significant physiological and immunological differences between human and animal lungs, which leads to inconsistent translation to human disease. Microengineered lung-on-a-chip platforms have been created to mimic the structural and functional features of the alveolar and small-airway niches in order to get around these restrictions. These systems mimic mechanical strain, physiological airflow, and the air-blood barrier. These devices have been widely used to study cigarette smoke, an established risk factor for lung cancer and chronic obstructive pulmonary disease (COPD). Cigarette smoke extract (CSE)-induced COPD-related injury has been modelled using micropillar arrays that can apply cyclic mechanical deformation. Results show that CSE disrupts intercellular junctions, activates airway epithelial cells, downregulates IL-6/JAK signalling via STAT3 modulation, and causes the epithelial-mesenchymal transition (EMT), which can be tracked by changes in apical junction complex (AJC)

gene expression. Pharmacokinetic analysis of aerosolised drug formulations, which provide better delivery efficiency and less invasiveness, is also made possible by lung-on-a-chip technology. Timothy et al. demonstrated that aerosolised insulin showed decreased adsorption and increased molecular aggregation during transport across the chip's barrier, with aerosolisation promoting insulin fibril formation, using a microfluidic bilayer device with an air-liquid interface. These results emphasise how crucial microphysiological systems are for evaluating aerosol treatments in environments that closely resemble human lung physiology. Additionally, lung-on-a-chip platforms have been widely used to represent both chronic respiratory illnesses and acute and infectious lung ailments, such as COVID-19 and acute respiratory distress syndrome (ARDS). These devices provide a full investigation of virus entry, host-pathogen interactions, and cytokine-mediated inflammatory responses by modelling the alveolar-capillary interface under dynamic fluid flow and mechanical strain. In particular, lung-on-a-chip models have been used to study immune cell recruitment, endothelial dysfunction, and SARS-CoV-2 infection, providing crucial insights into the progression of the illness and the evaluation of treatments. Similarly, ARDS models on chips have facilitated studies on pulmonary oedema, barrier breakdown, and inflammatory signalling under physiologically suitable settings.^{27,28}

Kidney-on-a-chip

Drug-transporter interactions have a major impact on drug excretion and are essential to renal drug disposition. The kidney is extremely vulnerable to nephrotoxic injury because it is essential for removing endogenous toxins, metabolites, and xenobiotics. Post-marketing medication withdrawals can be decreased by accurately predicting transporter-mediated interactions. Human renal microphysiology cannot be accurately replicated by conventional nephrotoxicity assessments, which are based on static *in vivo* cultures, animal models, and clinical studies. A crucial factor influencing the morphology, polarisation, and transporter activity of proximal tubule epithelial cells (PTECs) is fluidic shear stress (FSS). Physiologically relevant FSS is incorporated into kidney-on-a-chip platforms, which usually have three interconnected microchannels: an extracellular matrix (ECM) channel, an adjacent perfusion channel for epithelial culture, and an apical and basolateral compartment that mimics tubular epithelium. To create controlled flow, some systems use passive levelling on a rocker platform. These microfluidic models accurately replicate *in vivo* renal injury by displaying dose-dependent disruption of the epithelial barrier and increased release of lactate dehydrogenase (LDH) upon exposure to cisplatin, a classic nephrotoxic compound. Important efflux transporters, such as multidrug resistance protein 4 (MRP4) and P-glycoprotein (P-gp), which are crucial for renal drug clearance, have also been assessed using kidney-on-a-chip devices. These platforms also make it possible to model renal dysfunction caused by viruses, which sheds light on the mechanisms underlying kidney failure linked to infection.^{29,30}

Heart-on-a-chip

The reaction of the cardiac cells and mechanical stress are the primary determinants of the heart's growth and function. Understanding the basic functioning of the heart is crucial for developing new, effective medications. The biological, mechanical, and physical processes of the heart are not well represented by the cell culture techniques used today. Studies have attempted to simulate the heart, however most of them are two-dimensional and, although they do show certain mechanical characteristics, they are not the most effective at faithfully simulating the human heart because they lack full heart properties and do not permit fluid flow or other comparable work. These heart-on-a-chip technologies provide a promising way to use the functional properties of the heart to generate drug screening platforms. The heart-on-a-chip is an excellent platform for drug screening and many other applications because of its electrical signals, anisotropic cell arrangement, fluidic flow, and ability to incorporate sensors for the evaluation of cardiomyocyte contraction, calcium transients, electrical action potential, and stress response. Other features include the introduction of cyclic stretch to recreate the microenvironment. The correct cell types must be selected in order to produce a model that is functionally helpful.^{31,32} The ridges were positioned on the flexible muscle substrate to produce anisotropic heart tissue. The device is also used to study the effects of endothelial extracellular vesicles (EEV) on the contraction of human laminar cardiac tissues. The study offered strong proof of the cardioprotective impact of EEVs against ischaemia-reperfusion loss by lowering the mortality and contractile activity of cardiac cells. The electrophysiology of cardiac cells may be continuously monitored by the integration of extracellular and intracellular bioelectronics. In order to investigate how acute hypoxia affects heart functions, Haitao Liu and colleagues created a microfluidic device that is combined with extracellular and intracellular bioelectronics. The fluidic system replicates the ischaemic conditions caused by coronary artery occlusion by changing the temporal oxygenation of the culture media. Additionally, cardiotoxicity assessment has made substantial use of heart-on-a-chip platforms, which allow the study of drug-induced effects on cardiomyocyte contractility, electrophysiological activity, and total cardiac function under physiologically relevant haemodynamic settings. Notably, these platforms make it easier to identify biomarkers for myocardial damage, proarrhythmic hazards, and dose-dependent cardiotoxic reactions that are frequently missed in traditional *in vitro* models. Heart-on-a-chip devices greatly improve the safety and effectiveness profiles of cardiovascular drug research by offering a predictive and clinically transferable platform for identifying adverse cardiac events.^{33,34}

Chipped liver

The OOC platforms have gained significant traction since they are the most similar in contrast to the conventional methods, to examine the human cell-microenvironment. Additionally, toxicity testing without animal use might lessen ethical problems.

Furthermore, the liver's important role as an organ for the oxidation and purification of xenobiotics and toxicants has fuelled the development of *in vivo* platforms like liver-on-a-chip in recent years. Multiple cell systems on a liver-on-a-chip can be used to understand various liver molecular pathways, evaluate toxicity, and simulate illnesses. For example, the development and manifestation of alcohol-induced liver disease (ALD) depend on non-parenchymal cells. A liver-on-a-chip technology has been successfully developed to understand how various hepatic cell types communicate with one another as ALD advances, using both parenchymal and non-parenchymal cells.^{35,36}

Neural system-on-a-chip

The physical structure and numerous chemoelectrical and electrical characteristics of the neural system enable the brain to store, retrieve, and transfer information in order to regulate the function of organs and tissues. De novo brain systems have recently been designed using microdevices, with a focus on spatiotemporal recordings of electrophysiological signals. In addition to better understand this complex bioelectric network, these technologies may also shed light on neurological disease problems.^{34,35} Separating cellular structures from other cells or populations of cells from one another has been a crucial microengineered method for researching brain communication and network development. From tissue engineering to cellular biosensors, the location and proliferation of neurons are crucial in many domains. Surface modification is frequently used to separate and culture neurons while permitting neurite outgrowth in order to assess neuronal outgrowth capacity under various settings. This can be done through physical constraints such as microgrooves or channels or sticky substrate patterns. Although the architecture of *in vivo* brain networks cannot be replicated by these systems of extension, they will be utilised for physical and molecular research. In order to create brain layers and 3D architecture, the 3D microfluidic devices and division have also been employed in the creation of guiding 3D structures for neural engineering. Kunze et al. demonstrated the ability to create hierarchical scaffolds with implanted original cortical neuron layers using agarose-alginate mixtures divided by cell-free layers. In order to create concentration gradients that induced enhanced neurite outgrowth, B27 supplementation was administered. Early phases of network creation within the three-dimensional frameworks and the use of division to facilitate 3D-directed outgrowth were demonstrated by the directed neurite outgrowth to other neurite-rich locations. Although the technique promises to produce more *in vivo* like brain tissues and networks, additional system development is still required to provide these cell mimic cultures more functionality.³⁷

Brain-on-a-chip

Additionally, understanding the various mechanisms involved in drug delivery applications such as receptor-mediated transport, adsorptive-mediated delivery, inhibition of efflux transport, and various BBB disruption techniques like sonoporation and

Table II: Characteristics and applications of various OOC

Chipped organ	Uses	Cell type	Ref
Alternatives of the liver and testis working together using a multi-OOC	Male reprotoxicity and the relationship between the liver and testes.	Primary human adult testicular cells, primary human hepatic stellate cells, and HepaRG.	41,42
Model of cartilage-on-a-chip	For researching the mechanical elements that contribute to the aetiology of osteoarthritis (OA) and for creating medications to treat the condition.	hACs, or human articular chondrocytes.	
Corneal barrier on a microchip	To speed up the creation of ophthalmic medications by analysing the impact of the eye's twitching creates shear strain on the corneal membrane.	HCE-T, or human corneal epithelial cells.	43
On-a-chip Duodenum Intestine	For the preclinical evaluation of medications. For validation, the authors used 1,25-dihydroxyvitamin D3 (VD3), DMSO, and rifampicin.	Endoscopic biopsies and basic human intestine microvascular endothelial cells (HIMECs)	44
Chipped prostate gland	To comprehend how the human prostate gland's epithelial and stromal interface interact.	Benign human prostate stromal cell lines (BHPs1s) and basic human prostate baseline epithelial cells (PrECs).	45
Oral mucosa on a microchip	For examining how microorganisms and substances interact with the oral mucosa.	Both immortal human gingival keratinocytes and human gingival fibroblasts (Gie-No3B11).	46
Mode of a multicellular intestine-on-a-chip	To validate 2-[(aminocarbonyl)amino] and comprehend the inflammatory process. The anti-inflammatory medication -5-(4-fluorophenyl)-3-thiophenecarboxamide (TPCA-1).	Enterocytes (Caco-2), immune cells (THP-1 and/or MUTZ-3), and goblet cells (HT29-MTX).	47
Chip made of bone marrow	For examining how the niche interacts with both healthy and cancerous haemopoietic cells.	Human bone marrow mononuclear cells (BMNC) and specific BMNC-differentiated cells (also known as MSC, or Stro1+ mesenchymal stromal cells), sinusoidal endothelial cells (SEC), artery endothelial cells (AEC), and partially developed osteoblasts.	48
Adipose-on-a-chip	For investigating how immunity and metabolism interact in people with type II diabetes.	The pre-adipocytes and mononuclear cells of U937.	
Hair-and-skin-on-a-chip	During a prolonged culture period, a multi-organ system with dynamical perfusion and fluctuating dynamic shear stress.	Ex vivo frontal and temporal scalp skin follicular unit extraction and biopsy were used to compare the prepuce and skin of human adolescents.	49
Placenta-on-a-chip	To investigate how being around TiO2 nanoparticles affects the barrier that surrounds the placenta.	Human choriocarcinoma BeWo cells, HUVEC.	50

electroporation is made possible by the physiologically required reconstruction of the blood brain barrier (BBB). An *in vivo* brain model called the brain-on-a-chip model is used to evaluate the neurotoxicity of drugs and look into the root causes of neurological conditions. This model may also be used to study how neurons migrate in response to chemotactic stimuli. The network of interactions between the brain's neurons, astrocytes, microglia, and oligodendrons makes it challenging to create *in vivo* brain-chip model. A membrane separates the bottom brain environment channel, which contains human astrocytes (HA) in Matrigel and human brain vascular pericytes (HBVPs), from the top vascular layer, which contains human brain microvascular endothelial cells (HBMEC), and contains unique receptors for intermediate transcytosis with high-density lipoprotein (HDL)-mimetic nanoparticles. The system has shown reduced expression of polarised aquaporin-4 (AQP4), a three-dimensional astrocyte network, and reactive gliosis hallmarks. A brain-on-a-chip platform for researching the causes and progression of neurological diseases like Alzheimer's, multiple sclerosis, Parkinson's, nerve injury, and neuro-inflammatory diseases has been made possible by the development of stem cell engineering and complex

microphysiological systems. This will help in the development of new drugs. Interactions between cells, stem cells, and cell-matrix spatial gradients of chemicals have been shown in a number of brain-on-a-chip models.³⁸

Pancreas-on-a-chip

Simulating the pancreatic interface and function *in situ* provides relevant data for human physiology, unlike human cell culture models. Through OOC technologies, pertinent mechanical cues, the issue-tissue contact necessary for cell signalling, and cellular crosstalk can all be given. The intrinsic characteristics of microfluidic devices, perfusion and fluid flow, for example, provide a systemic reaction found in actual biological settings. Drug research initiatives can be accelerated by these miniature models. Animals with pancreas-on-a-chip can be used to study diseases linked to cystic fibrosis and diabetes. In one of the pancreas-on-chip prototypes, KyuShikMun and colleagues replicated cystic fibrosis (CF) in a co-culture microfluidic system barrier using islet cells and pancreatic ductal epithelial cells (PDECs) divided by a thin, porous membrane. Table II lists additional OOC types.^{39,40}

OOc in cancer treatment

Since the tumour microenvironment provides biochemical and spatiotemporal cues that drive the transition from small cell clusters to malignant phenotypes, it is crucial for understanding tumour progression even though it is challenging to replicate *in vivo*. By encouraging angiogenesis, changing the composition of the extracellular matrix, and improving the recruitment of fibroblasts and immune cells, non-malignant stromal components have a substantial impact on the development and spread of carcinoma.^{51,52} By enabling size-dependent and spatiotemporal analysis, including bidirectional cell migration under physiologically relevant nutrient perfusion, microfluidic systems allow for the controlled study of these interactions. Multicellular tumour spheroids (MCTS), in particular, are three-dimensional models that exhibit realistic metabolic gradients and resemble avascular tumour regions. By producing consistent MCTS arrays and facilitating dynamic perfusion, microfluidic devices enhance nutrient exchange and make anticancer drug screening more accurate.⁵³

Precision medicine with OOC

Precision medicine can benefit from the development of microfluidics. Through the use of primary human cells, cells produced from stem cells, or a microenvironment that has medically suitable conditions, an optimal customised system may give unique physiology. Using microfluidic devices in pre-clinical research helps speed up drug efficacy evaluation, ADME investigations, and toxicity screening of new treatments. The majority of medications on the market do not produce the desired results in all individuals, and some people are given medicine that is ineffective or even harmful to their health. Such hazardous therapies must be avoided in this situation, and medications must be customised to meet the needs of the patient to improve their quality of life.^{54,55}

Pharmacokinetics/pharmacodynamics (PK/PD) examinations

A drug's pharmacokinetic (PK) properties, which must be understood early in the drug development process, significantly influence its pharmacological effects. The inability of traditional *in vivo* testing to precisely duplicate current PK modelling techniques is a major drawback that contributes to inaccurate drug toxicity prediction. While PK/PD parameter forecasting mathematical models can be extended to include *in vivo* research in animal models and then human clinical trials, these sequential procedures are expensive, time-consuming, and subject to strict ethical regulations. Furthermore, the models that are now in use have a number of shortcomings that restrict their wider use. Specifically, since they lack multi-organ architectures that adequately simulate the complexity of human physiology, traditional *in vivo* models used for medication toxicity and efficacy assessment often fail to accurately estimate drug pharmacokinetics. Microfluidic PK/PD platforms have been designed to reproduce drug absorption,

metabolism, and systemic reactions under controlled settings in order to overcome these constraints. In order to provide a more physiologically relevant framework for PK/PD assessment, Shuler and Sung⁵⁶ created microfluidic multi-organ models that allowed for the simultaneous investigation of drug distribution and metabolism across interconnected tissue compartments. In addition, Imura et al.⁵⁷ demonstrated the usefulness of gut-liver axis modelling in forecasting first-pass drug metabolism by presenting an integrated microfluidic system that combined intestinal absorption and hepatic metabolism functions. Together, these systems overcome the translational constraints of traditional *in vivo* and *in vitro* methods and provide enhanced predictive power for drug toxicity mechanisms and metabolic profile, advancing pharmaceutical research and development.⁵⁸

Prospects and challenges of OOC in the future

OOc small systems have the potential to make a big impact on the future of the pharmaceutical industry, since they can expedite the drug development process and eliminate the requirement for animal models to evaluate toxicity and efficacy. Regulatory pressure to lower healthcare costs, shrinking pipelines, and growing R&D expenses are currently plaguing the scientific and pharmaceutical sectors. Some medications even experience withdrawal after going on sale, and later, more expensive clinical phases of drug research are plagued by expensive, high attrition rates. Today, one of the main obstacles in the medication development process is the high cost and duration of animal testing, which is necessary to determine therapeutic effectiveness and safety. It also requires a number of substances that aren't always available in the beginning.^{59,60} Verifying that each organ chip exhibits the anticipated cellular response to that hormone, expresses the proper amounts of each hormone receptor, and has the proper rhythmic control of the impacted physiological processes will be crucial. Examining the alterations in an organ's metabolomic and signalling profile that might be brought on by external hormone regulation non-invasively using ion mobility-mass spectrometry or other high-throughput analytical methods, will be intriguing and simple. For instance, if specific optical reporter genes are present in the cells that make up the organ-chip tissues, it will be possible to track changes in gene expression. However, it is currently impossible to follow large sets of genes without killing them because organ chips are now much more expensive than mice. The technologies being studied may offer more accurate human-relevant models for assessing toxicity and efficacy, in addition to offering insight into the mechanisms of action at the tissue and organ levels. Many drug candidates' absorption, dispersion, metabolism, and elimination (ADME) may already be predicted using *in vivo* human cell-based models. For example, primary human hepatocytes can be used to predict drug-drug interactions in humans.^{61,62}

Regulations as per FDA

By amending the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355), the FDA Modernisation Act 2.0 has greatly accelerated the

adoption of OOC technologies in drug development. According to the amendment, sponsors may assess the safety and efficacy of drugs using contemporary, human-relevant techniques, such as cell-based assays, microphysiological systems, organ chips, sophisticated computational models, and other non-animal test methods. Innovative platforms that closely mimic human biology, like OOC and 3D *in vivo* models, are now legitimate as viable substitutes for conventional animal testing thanks to this regulatory change. OOC systems provide more accurate predictions for pharmacological and toxicological reactions by simulating vital physiological processes of organs like the liver, lung, and heart. It is anticipated that the Act will expedite these technologies' development, validation, and industry adoption, allowing for more accurate evaluations of potential medications. In the end, more widespread use of OOC platforms can lower costs, shorten time-to-market, lower development failures, and give patients quicker access to safer and more effective treatments.^{63,64}

Applications of OOC

The quick development of OOC technologies, which are based on tissue engineering and microfluidics, has greatly improved pharmaceutical development, especially in PK/PD analysis, drug screening, toxicity assessment, and efficacy evaluation. Additionally, these platforms facilitate patient-specific analyses and the creation of intricate disease models, which lowers inter-individual variability and advances personalised precision medicine. OOCs offer a revolutionary substitute for traditional 2D cultures and animal models. Conventional monolayer cultures are limited in their capacity to replicate dynamic tissue environments because they lack mechanical cues, extracellular matrix complexity, and physiological shear forces. Despite their widespread use, animal models frequently have low translational relevance because of species-specific variations. By combining biomimetic materials, multi-cell co-cultures, and regulated microfluidic flow, OOCs get around these restrictions and more accurately replicate human organ-level functions.⁶⁵ Another important use of OOC platforms is disease modelling. Complex pathological microenvironments involving inflammation, barrier disruption, mechanical stress, or biochemical gradients are difficult for conventional models to replicate. OOCs make it possible to simulate physiological processes in real time, including peristalsis, breathing motions, vascular flow, and three-dimensional tissue architecture. For example, human respiratory mechanics and inflammatory responses have been replicated by lung-on-a-chip devices, providing insights not possible in animal systems. Additionally, by simulating inter-organ communication, multi-organ or body-on-a-chip systems increase OOC capabilities. Animal physiology frequently deviates from human metabolic pathways, and conventional *in vivo* models are unable to replicate systemic processes like absorption, distribution, metabolism, and excretion (ADME). By enabling physiologically relevant evaluation of drug metabolism, multi-organ toxicity, and pharmacological interactions, linked organ chips such as liver-heart and liver-kidney models improve predictive accuracy for human applications.

Limitations of OOC

OOC systems have a number of drawbacks that prevent their broad use and translational applicability, despite their many benefits. Lack of uniformity and technical complexity are two of the main issues. OOC device manufacturing frequently uses specific materials and methods that are not yet widely standardised, which results in inconsistent device performance and poor laboratory repeatability. Furthermore, it is still challenging to fully replicate the intricacy of human organ physiology. The integration of various organ systems is another significant constraint. Although the goal of multi-organ-on-chip platforms is to replicate systemic interactions, it is technically difficult to scale various organ models suitably and preserve physiologically relevant communication between them. This integration is made more difficult by variations in flow rates, cellular needs, and microenvironmental circumstances. The development and use of OOC technologies are also hampered by ethical and legal issues. These include concerns about data privacy, intellectual property rights, and the usage of patient-derived cells. Moreover, the acceptance of OOC-based models in drug approval procedures is restricted by the lack of clear regulatory frameworks. High fabrication and operating costs limit accessibility for ordinary laboratory use, and insufficient immune system representation limits the capacity to explore complicated immune responses. In order to advance OOC systems toward wider clinical and industrial applications, these restrictions must be addressed.⁶⁶

Market size of OOC

Chipped organs market size was estimated to be worth USD 116.5 million in 2023, is projected to grow to approximately USD 1.4 billion by 2032 due to the growing need for more precise and trustworthy *in vivo* models of human organs for toxicity testing, disease modelling, and drug development. North America was predicted to lead the market in 2023, followed by Europe, and this trend is anticipated to persist throughout the forecast period. North America is credited with a number of things, including the existence of major pharmaceutical corporations and the introduction of novel and sophisticated organs-on-chips to the market for favourable government programmes and financing initiatives for the creation and study of fundamental drugs.⁶⁷ By developing and modifying OOC technology, several important firms in the area are attempting to improve the expensive and time-consuming drug development process. Both governmental and commercial institutions are investing a lot of money on research. By 2026, it is anticipated that the worldwide OOC market would have grown from its 2020 size of around USD 41 million to USD 303.6 million. Over the next seven years, the liver and kidney segments are anticipated to rise at compound annual growth rates (CAGRs) of 35.4% and 36.1%, respectively. The growth of OOC technology is primarily driven by a focus on alternatives to animal testing models and an expansion of early drug detection partnerships between OOC producers and pharmaceutical corporations. North America is anticipated to hold the greatest

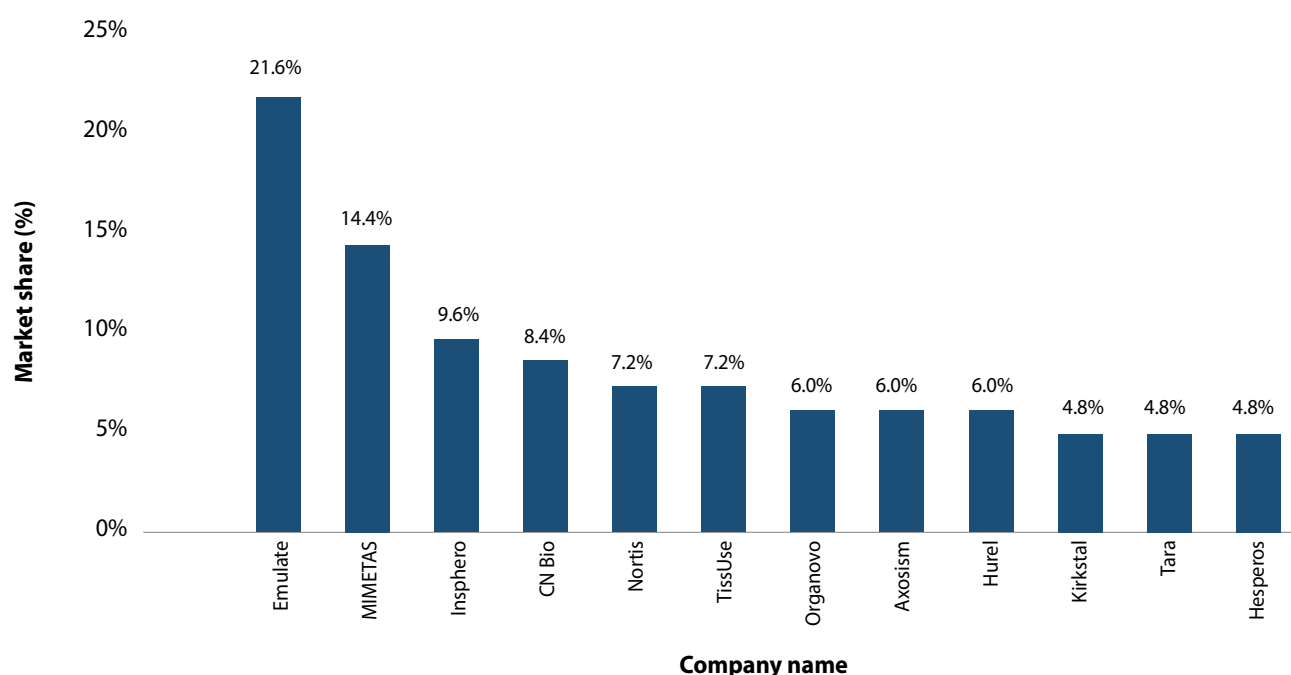


Figure 2: Manufacturers involved in OOC development

market share during the forecast period, while Asia-Pacific (China, India, and Japan) is anticipated to grow at the fastest rate as mentioned in Figure 2.⁶⁸

Conclusion

Driven by advances in microfluidics and tissue engineering, OOC technology is a significant breakthrough in disease modelling, toxicity testing, and drug discovery. Through integrated sensing components, these platforms support real-time monitoring of cellular and biochemical parameters while allowing controlled fluid circulation to replicate systemic physiological responses seen *in vivo*. Without sacrificing tissue integrity or cell viability, this non-invasive monitoring improves data quality. However, the proper cell selection, optimised flow rates, and accurate microchannel dimensions to guarantee physiologically relevant microenvironments are crucial for the effective design and operation of OOC systems. OOC technologies provide more accurate models of human organ function by replicating dynamic biochemical gradients and intricate, multicellular architectures. Their transformative potential is highlighted by their capacity to accelerate drug development pipelines, assess drug toxicity with greater predictive accuracy, and simulate uncommon disease conditions. Additionally, by enabling customised therapeutic testing and forecasting patient-specific responses, patient-derived OOC platforms have great potential for personalised medicine. OOC platforms provide a highly predictive, effective, and human-relevant substitute for advancing therapeutic development and biomedical research.

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Conflicts of interest

The authors declare no conflict of interest.

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Artificial Intelligence in clinical trials: a game changer

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Abstract

Clinical trials are a series of systematic investigations designed to test new treatments or interventions aimed at treating or preventing diseases and serious medical conditions. Typically conducted in four distinct phases, these trials involve both animal models and human participants. Developing and delivering a new drug to the market is an intensive and costly process, often taking 12–15 years and requiring approximately \$12 billion. Given this prolonged timeline, patients in urgent need cannot afford to wait over a decade for effective treatments. In this context, Artificial Intelligence (AI) emerges as a transformative approach, offering transformative potential to revolutionise the clinical trial landscape. AI technologies can significantly reduce both the time and cost required for drug development by streamlining processes such as patient recruitment, trial design, data analysis, and monitoring. By improving efficiency and enabling predictive risk mitigation, AI enhances decision-making throughout the trial lifecycle. This study presents a comprehensive overview of how AI is being integrated into clinical trials, emphasising its role in overcoming traditional challenges, minimising risks, and accelerating the path to market. As a result, AI is not just an advancement—it is redefining the future of clinical research.

Keywords: Artificial Intelligence, clinical trials, drug development, risk mitigation, software

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Introduction

Artificial Intelligence (AI) is at the forefront of the Fourth Industrial Revolution (Industry 4.0), which is reshaping the global landscape through advanced automation, big data analytics, and intelligent technologies. AI is a branch of computer science concerned with creating machines capable of performing tasks that typically require human intelligence. These tasks include learning from experience, understanding natural language, recognising patterns, and solving complex problems. At its core, AI leverages techniques such as machine learning (ML), natural language processing (NLP), neural networks, and predictive analytics to emulate human cognition.¹ The development of AI has been influenced by multiple disciplines, including computer science, psychology, physiology, neuroscience, sociology, biology, and mathematics. These fields contribute to AI's ability to process and interpret massive amounts of data in real-time. From its early conceptualisation to recent breakthroughs in deep learning and autonomous systems, AI has evolved rapidly. Significant milestones include the introduction of the Turing Test (1950), the coining of the term "Artificial Intelligence" by John McCarthy in 1956, the development of early neural networks, and the deployment of emotion-expressing robots like Kismet.² A brief overview of the historical timeline of AI development is presented in Table I.

AI's integration into health care has grown remarkably in the past decade. It has revolutionised diagnostics, treatment planning, robotic surgeries, and personalised medicine. Among these advancements, one of the most promising applications is in the domain of clinical trials. Clinical trials are a cornerstone of the drug development process, ensuring that new treatments are safe and effective before reaching the market. However, they

are also known for being lengthy, costly, and complex, often requiring more than a decade of research and billions of dollars in investment. Traditional clinical trials face numerous challenges, including patient recruitment difficulties, high dropout rates, inefficient data management, delayed reporting, and stringent regulatory demands. Nearly 80% of trials fail to meet enrolment timelines, and 30% of phase III trials are terminated due to lack of patient participation. These setbacks delay innovation and limit patient access to timely therapies. The application of AI to clinical trials is emerging as a transformative solution to these persistent challenges. AI technologies have the potential to streamline the entire clinical trial lifecycle from protocol design and patient recruitment to monitoring, data collection, and regulatory submission. AI-driven platforms can rapidly analyse electronic health records (EHRs), genetic information, and real-world data to identify eligible participants who meet trial criteria. This improves recruitment efficiency, enhances diversity, and reduces dropout rates through personalised follow-up strategies.^{3,4}

AI enhances clinical trials by enabling real-time monitoring, improving data accuracy, and supporting early detection of adverse events through integration with wearable devices and electronic systems. It also facilitates adaptive trial designs and predictive modelling, improving trial efficiency and outcomes. However, challenges such as data privacy, algorithmic bias, and regulatory concerns must be addressed. This study aims to review the role of AI in improving efficiency, data management, patient engagement, and outcome prediction in clinical trials. By addressing the barriers inherent in traditional clinical research, AI is not merely an auxiliary tool but a disruptive force, a transformative technology in the development of safer, faster, and more accessible medical treatments.⁵

Table I: History related to AI*

Year	Action
1923	"Rossum's Universal Robots" (RUR) in London, first use of the word "robot" in English through Karel Capek's play.
1943	Foundations were laid for neural networks.
1945	The term <i>Robotics</i> was coined by Isaac Asimov, a Columbia University alumnus.
1950	Introduction of Turing Test which is used for evaluation of intelligence and published " <i>Computing Machinery and Intelligence</i> " by Alan Turing.
1956	John McCarthy coined the term <i>Artificial Intelligence</i> . Demonstration of the first running AI program at Carnegie Mellon University.
1958	John McCarthy invents LISP programming language for AI.
1969	Stanford Research Institute Scientists Developed " <i>Shakey</i> ", a robot, provided with perception, locomotion, and problem solving.
1979	Stanford Cart, the first computer-controlled autonomous vehicle, was built.
1985	Harold Cohen created and demonstrated <i>Aaron</i> , the drawing program.
1990	AI's major innovations include: • Demonstrations of machine learning • Web Crawler, Data mining • Translation and understanding natural language • Virtual Reality, Vision • Games • Case-based reasoning • Multi-agent planning • Scheduling
2000	Availability of Interactive robot pets commercially. MIT displays <i>Kismet</i> , a robot with a face that expresses emotions. The robot <i>Nomad</i> explores remote regions of Antarctica and locates meteorites.

*This table highlights major milestones in the evolution of Artificial Intelligence, from the early concept of robots to advanced autonomous systems and emotionally responsive machines.

Objective of the study

The objective of this study is to critically evaluate the role of AI in clinical trials, focusing on its applications in patient recruitment, trial design, data management, and outcome prediction. The study also aims to analyse the advantages and limitations of AI, along with the ethical and regulatory challenges associated with its integration in clinical research.

History of AI

See Table I.

AI in clinical trials

Clinical trials

According to the WHO, a clinical trial is defined as "a research study that prospectively assigns human participants or groups to one or more health-related interventions to assess their effects on health outcomes." Clinical trials are generally conducted as four different phases. Figure 1 illustrates the design of clinical trials across four phases: Phase I (safety), Phase II (efficacy), Phase III (large-scale validation), and Phase IV (post-marketing surveillance).⁶ It also highlights the role of AI in each stage, including protocol optimisation, patient recruitment using electronic health records, real-time monitoring, and data analysis.

Challenges faced in conducting clinical trials

Challenges and ethical considerations

Generative AI is being rapidly adopted. The widely used ChatGPT had over 180 million active users at the time of the think tank, and a third of US adults 18 to 64 years old now use generative AI every week. Generative AI is commonly being used for applications such as document generation. As these technologies mature, the use of generative AI is expected to increase significantly, becoming more prevalent in clinical settings and more familiar to research participants. The pace of adoption underscores the urgency for organised, informed, and strategic integration of

Table II: Description of different phases of clinical trials*

Sl. No.	Description	Phase-1	Phase-2	Phase-3	Phase-4
1	Terms	Human Pharmacology	The exploratory	Therapeutic conformity	Post marketing
2	No. of subjects	20–100	100–500	1 000–5 000	N/A
3	Studies conducted	Safety Human Pharmacokinetics and Pharmacodynamics Dosing range	Safety Efficacy Dose selection	Safety Efficacy	Pharmacovigilance Post-Marketing changes
4	Time period	Weeks to months	Several months to two years	Four to five years	Several years
5	Types of subjects	Healthy volunteers	Subjects with disease	Subjects with disease	Subjects with disease
6	Success rate (Approximately)	70%	35%	25–30%	N/A
7	Notes	Safety check to carry out efficacy studies.	Determines effectiveness of drug	determines drug's therapeutic effect on subject	Watch the drug's long-term effects.

*Clinical trial phases move systematically from initial safety testing to large-scale efficacy validation and continuous post-marketing safety surveillance.

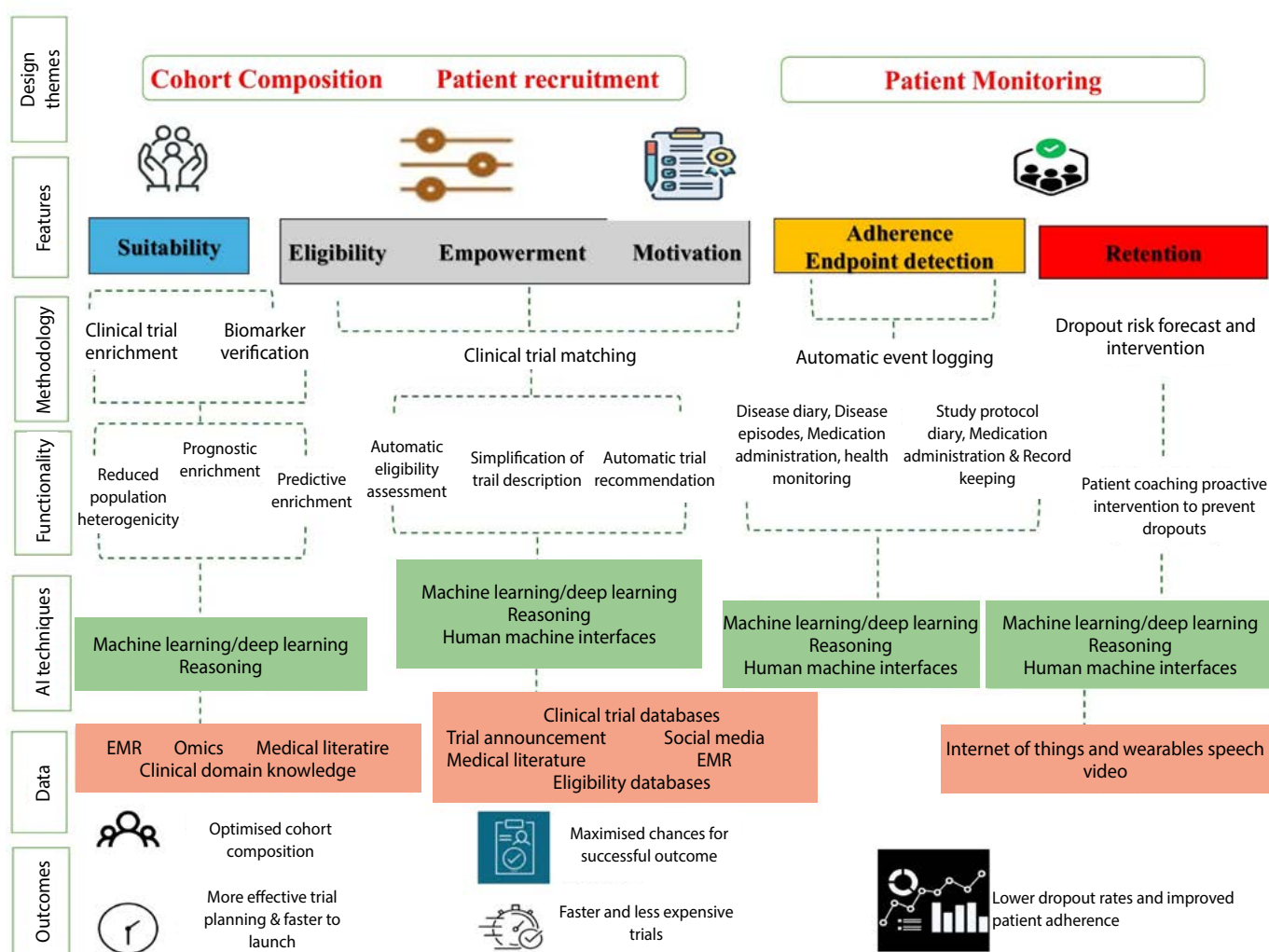


Figure 1: An overview of clinical trial design on Artificial intelligence in clinical trials

AI-driven clinical trial design streamlines patient selection, predicts treatment outcomes, and enhances safety through real-time monitoring. AI tools optimize protocols, reduce trial duration, and improve precision in developing new therapies.

Table III: Potential impacts of generative AI on clinical research processes*		
Clinical Research Process	Current approach	Potential changes introduced by generative AI
Incremental improvements		
Document generation	Manual creation of research tools and documents	Generation of drafts by AI, speeding up document creation and ensuring consistency
Participant engagement	Traditional methods for recruitment and dissemination of results	Direct engagement through AI, from recruitment to results sharing, making the process more inclusive and efficient and improving retention
Potential transformative changes		
Clinical trial design	Design based on historical data and standard practices	AI-simulated scenarios and optimised protocols, increasing the success probability of clinical trials
Informed consent process	Standardised documents and procedures, often not fully tailored to individual comprehension levels	Facilitation of a more personalised, engaging consent process through advanced technologies such as chatbots or avatars
Data collection, analysis, and synthesis	Reliance on conventional data gathering and analysis techniques	New avenues for AI-driven data collection and synthesis, enhancing accuracy and depth of research findings
Ethical and bias mitigation	Policy and standard practice, with varying degrees of effectiveness	Proactive efforts via AI to identify and correct biases in data and research practices, even within AI tools themselves, reinforcing equity and ethical integrity
Data management and security	Management through established IT protocols and practices, which involves challenges in data discoverability and reusability	AI-enhanced data management, ensuring data quality, privacy, discoverability, and security, while upholding research integrity and reproducibility standards

*Generative AI supports automated protocol design, literature review, and hypothesis generation, improving study planning efficiency.

AI-informed tools into clinical research.⁷ Before technologies become fully embedded, the full spectrum of benefits and harms that generative AI has within the clinical research domain should be systematically assessed. Without sharing experiences, both positive and negative, the field runs the risk of creating random practice without truly improving it. The speed of implementation must be carefully balanced with the need for rigour, safety, and caution.⁸

Achieving the full potential of generative AI via safe and effective adoption must account for the unique risks of generative AI: generation of misleading or erroneous output (hallucinations), inappropriate sharing of protected health information, coercive engagement, perpetuation of bias, limitations in interpretability, inaccurate broad generalisation from limited training data, and human overreliance on models. Risks must be sufficiently mitigated so that the foundation for using generative AI in clinical research is trustworthy according to ethical, technical, and regulatory considerations.⁹ The vast potential for generative AI to interact with research participants must be balanced with the imperative to preserve participant autonomy and maximise

the generalisability of results. Chatbots that allow for personalised communication increase engagement, yet the risk is that communication might become coercive or manipulative. This could reduce the voluntariness of consent and introduce bias in participant responses. Generative AI's ability to recreate its training data, potentially revealing individual patient information, creates confidentiality risks. Additionally, acceptable boundaries regarding which data are usable must be determined. Generative AI can train on vast amounts of input, including the entire digital footprint of participants such as social media patterns, which could help predict mental health status or cardiovascular risk. However, the extent to which these data can be used for disease prediction or trial outcomes must be agreed upon across all stakeholders.¹⁰

Beyond concerns related to the acceptable use of data, careful consideration of training data is critical to avoid perpetuation of bias. For example, the commonly used Generative Pretrained Transformer model propagates racial and gender stereotypes across clinical use cases, consequences of which have included overestimating the prevalence of HIV in Black patients and prioritising a diagnosis of panic disorder for women, but not men,

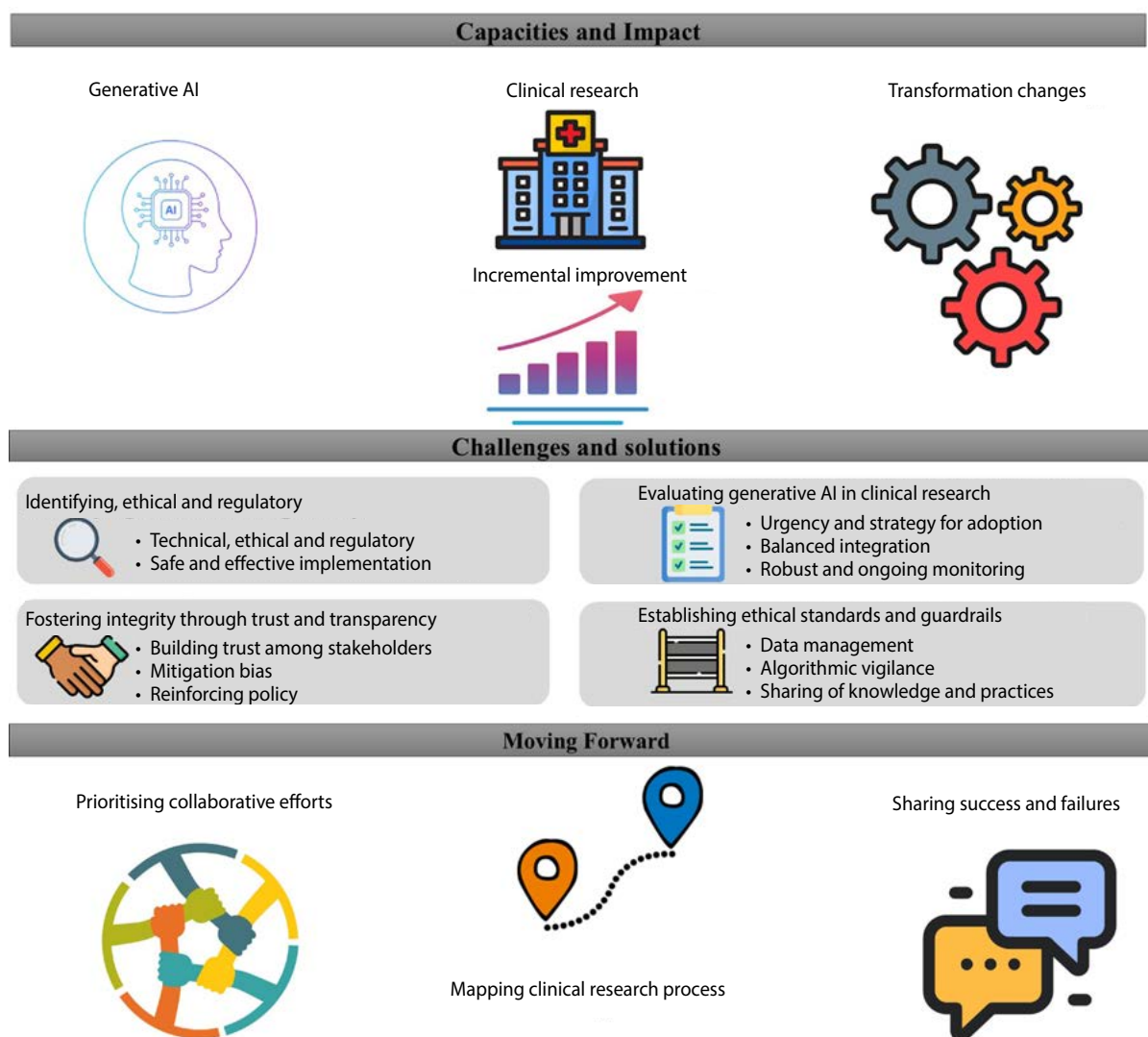


Figure 2: Impacts of Generative AI on Clinical Research

presenting with shortness of breath. Diagnostic accuracy is at risk, even when models reveal their biases. If uncorrected, such biases would have deleterious implications across the clinical research spectrum, including in how generative AI interacts with participants, how it is used to interrogate existing data, and how it is used to generate new data. Most critically, bias in the clinical research process would systematically bake inequities into health care for generations to come and should be avoided at all costs.^{11,12}

From a technical perspective, generative AI is expected to achieve acceptable accuracy and relevancy over time. However, it has limitations, such as producing incorrect or misleading outputs (hallucinations), and its performance may degrade, particularly if trained on biased or outdated data. The dynamic performance of generative AI will necessitate continuous surveillance throughout the use lifecycle. Robust monitoring will require human oversight and may demand the development of additional AI tools to help assess model performance. Further, new metrics for model evaluation and benchmarking are needed, especially given the nondeterministic nature of generative AI outputs. Transparency in model development and the data used for training are crucial. Secure data sharing systems are essential to understand model limitations and ensure diverse patient data in model development. Additionally, while synthetic data created by generative AI can help simulate expected changes in population data, they must be used with caution to prevent unintentional leakage of personal health information. (Figure 2)

Figure 2 illustrates the impact of generative AI on clinical research, highlighting its role in improving document generation, patient engagement, trial design, data analysis, and ethical decision-making. It demonstrates how AI enhances efficiency, accuracy, and personalisation across the clinical trial process while also emphasising the need to address challenges such as bias, data privacy, and regulatory compliance.

Difficulties in patient recruitment

Patient recruiting is one of clinical trials' most critical obstacles. Finding the correct individuals who match specified inclusion criteria can be extremely challenging, especially in cases of uncommon illnesses or highly specialist therapies. Clinical trials sometimes require individuals with certain medical histories, genetic markers, or demographic features to guarantee that the research results are relevant and accurate. However, approximately 80% of clinical studies fail to fulfil recruitment objectives on time, resulting in delays and, in some circumstances, the research being terminated entirely. Recruiting patients for clinical trials can be difficult due to limited knowledge, regional constraints, and potential participants' hesitancy. Many patients may be ignorant of potentially useful studies, or they may reside far away from research institutions. Others may be concerned about side-effects, potential expenditures, or time demands. Addressing these recruiting challenges frequently necessitates considerable outreach and teaching efforts; nonetheless, even with these, trials may struggle to enrol enough people, thereby delaying trial progress.¹³

Time required to conduct the study

Clinical trials are notoriously time-consuming, with many requiring years to complete due to their multi-phase structure, which involves safety (Phase I), efficacy (Phase II), and large-scale testing (Phase III) to set up a treatment's safety and effectiveness. Following these steps, more time is needed for regulatory review before the treatment is made available to the public. Each phase has tight standards that need careful control, detailed data analysis, and close monitoring of patient results. Because the phases are consecutive, delays in one step might cause the entire timetable to be pushed back, reducing the availability of potentially lifesaving medicines. The extended term also puts a burden on the sponsoring organisation's financial and operational resources, which may have to make difficult decisions about whether to continue or pursue other opportunities.¹⁴

Dropout of subjects during the clinical study

Patient dropout, or attrition, is another significant difficulty in clinical research, particularly when a large proportion of patients do not finish the trial. High dropout rates might jeopardise the statistical reliability of the data, making it difficult to assess the treatment's safety and efficacy. Replacing volunteers in the middle of a trial may be costly and time-consuming, potentially altering the study's design and introducing bias. Dropouts can happen for a variety of reasons, including the difficulty of repeated visits, unforeseen side-effects, or personal situations like relocation or sickness. Participants may lose motivation throughout extended research, especially in placebo-controlled trials, where they may become frustrated if they believe they are not receiving the active medication. Researchers may utilise personalised communication and engagement tactics to keep participants interested and boost retention. AI-based predictive models can help identify patients at risk of dropout; however, their accuracy may be influenced by incomplete patient data and variability in individual behaviour.

Stringent regulations

Clinical trials must meet stringent regulatory standards established by authorities such as the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA). These restrictions are critical for patient safety and ensuring that therapies fulfil high effectiveness criteria before they enter the market. However, they add to the complexity and possibility for delays. Regulatory standards regulate the whole trial process, from design to data reporting and post-trial monitoring, mandating rigorous documentation and numerous layers of approval. The requirement for regulatory compliance differs by jurisdiction, making multinational trials more difficult and administratively onerous. While important, these regulatory hurdles add to the lengthier durations and greater costs of performing clinical studies.¹⁵

Cost of conducting clinical trial

Clinical trials are one of the most expensive aspects of drug research, with single studies costing anywhere from tens of

millions to billions of dollars, depending on their extent, duration, and complexity. The requirement for specialist staff, medical facilities, patient recruiting initiatives, data administration, and regulatory compliance all result in significant costs. Prolonged deadlines can raise costs, as delays in any step might result in added expenses for staffing, monitoring, and administration. Trials concentrating on uncommon diseases or complicated problems may have significantly bigger expenses due to the difficulty of recruiting proper volunteers and the necessity for extensive testing. For smaller pharmaceutical companies, these high costs can be a barrier to bringing innovative therapies to market, stifling medical research and patient care.¹⁶

Data collection

Collecting information is an important yet complicated element of clinical research. Researchers must collect detailed information on each participant's health, treatment response, side-effects, and other pertinent factors. To ensure that data is gathered properly, safely, and in accordance with regulatory standards, modern technology and secure storage solutions are required. Traditional approaches, such as manual data input and paper records, are prone to mistakes and discrepancies. Although digital technologies can help, integrating data from several sources—such as hospitals, electronic health records, and wearable devices is still difficult. Data quality is crucial since inconsistencies or mistakes might skew the trial's outcomes. Ensure data privacy and follow standards such as the Health Insurance Portability and Accountability Act (HIPAA) in the United States and the General Data Protection Regulation (GDPR) in Europe. Although AI enhances data collection and integration, issues related to data privacy, interoperability, and data standardisation remain significant challenges in clinical research.

Artificial Intelligence

Artificial Intelligence (AI) refers to the replication of human intelligence processes by machines, particularly computer systems. The AI system we are building is designed to receive a protocol document, scan it, and assess it for various characteristics of interest.

AI can mainly be used in three different ways in clinical research:

Make clinical trials intelligent

Protocols designed using AI using deep learning techniques help to determine the outcome of a trial using predictive algorithms.

Various activities include:

- Analysing historical operational data
- Predicting site performance
- Predicting trial outcomes
- Drug adherence monitoring
- Voice assisted technologies
- Centralised trial monitoring

Optimise clinical trial processes

Patient recruitment is a task for conducting any clinical trial whereas retention of subjects is quite challenging in which 30% is the expected dropout rate on an average. By taking out the EMR information of subject, referring through a physician's record, reading binary data through medical scans and images and comparing them to a study's exclusion and inclusion criteria, patients required for enrolment for the clinical trials can also be identified more effectively.

Making smarter decisions

All the data provided in the initial stages is ingested and reviewed which helps to determine the further stages of research and where the drug is more likely to succeed. It also provides the "Go, No-Go" decisions for the clinical investigator by using prediction algorithms. Despite its wide applications, the implementation of AI in clinical trials requires careful validation, as errors in algorithms or biased datasets can affect the reliability of outcomes.¹⁷

Software used in clinical research

The advancement of digital technologies has significantly transformed the clinical research landscape, enabling greater efficiency, accuracy, and compliance. Software tools play a critical role across all stages of clinical trials—from study design and patient recruitment to data management, statistical analysis, and regulatory reporting. These systems streamline workflows, support data integrity, ensure regulatory compliance, and enhance decision-making. The following classification outlines key software categories used in modern clinical trials, highlighting both conventional systems and AI-powered tools that are reshaping clinical research methodologies. Although AI-based software tools improve efficiency in clinical trials, their performance depends on system integration, data quality, and user expertise. High implementation costs and regulatory concerns may also limit their widespread adoption.^{18,19}

Antidote

This software helps bridge the gap between medical researchers and the people who need treatment. It also supports research by **accelerating clinical trials** and offering new treatment options.

This software is built on a **clinical trial matching platform** which includes:

- **Antidote match:** This acts as a search platform where patients can directly get the information where the trial is being conducted that is suitable for them.
- **Connect network:** A network of health communities equipped with the Match search engine on their websites offers access to millions of patients seeking treatment.
- **Antidote base:** Connects research sites with patients actively searching for clinical trials in their area.
- **Antidote bridge:** Antidote Bridge allows sponsors to create a study page in plain English, providing the details patients want

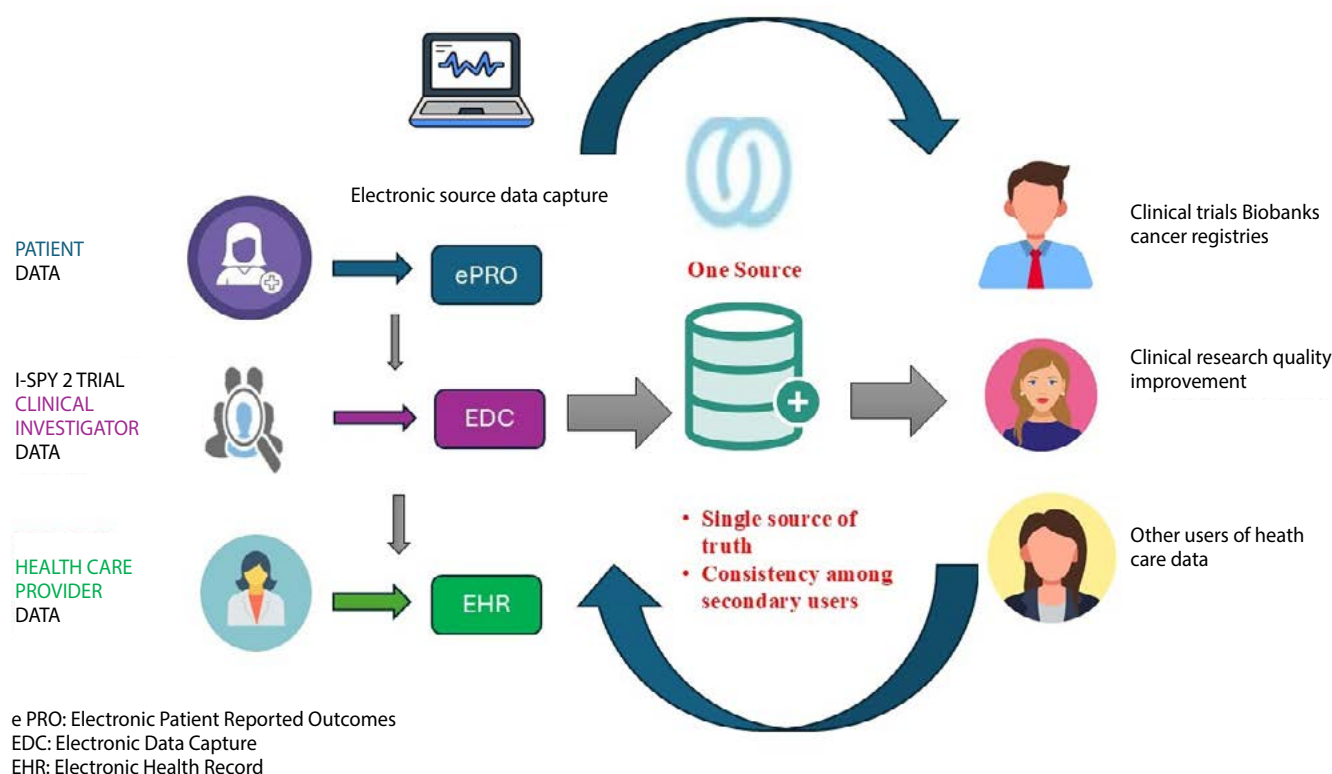


Figure 3: AI software's which are used during Clinical trials

AI software in clinical trials: Recruitment (Deep 6 AI), Design (Simcyp), Monitoring (ActiGraph), Data Analysis (IBM Watson Health), and Prediction (Sci-Kit Learn) streamline patient selection, safety, and outcome accuracy.

and need, for distribution to millions through health-related online platforms.²⁰

DEEP6 AI

This software enables rapid identification of eligible patients, reducing recruitment timelines from months or years to minutes. It supports clinical trial site selection through the analysis of real-time participant data and facilitates the generation of real-time study outcomes. Furthermore, it empowers patients by providing access to innovative treatment options and enhancing their involvement in treatment-related decision-making, thereby improving overall healthcare outcomes.

Figure 3 illustrates key AI-based software used in clinical trials, including tools for patient recruitment, trial design, monitoring, and data analysis. These platforms use technologies such as machine learning and natural language processing to improve efficiency, accuracy, and decision-making throughout the clinical trial process.

How it works

Your data + natural language processing + medical Codes + machine learning.

This DEEP6 AI works by combining AI with natural language processing and extracts clinical data such as symptoms, diagnosis and treatments, including lifestyle data and genomics. All the data

is transformed into unified patient graphs which in turn is helpful in matching the criteria of the trial being conducted.

TRIALS. AI: This software is mainly used to build the protocol for the clinical trial which is the primary objective to be considered when conducting any clinical trial. It optimises the cost, time required, and patient burdens and risks associated with the trial. It helps in optimising the trial protocol by minimising documents related to the trial and provides recommendations and points of interest.

Advanced AI techniques in clinical trials

Machine Learning (ML)

Machine Learning (ML) is at the forefront of AI advancements in clinical trials, enabling researchers to analyse extensive datasets with unprecedented accuracy and speed. By identifying hidden patterns and relationships within data, ML facilitates informed decision-making and enhances trial efficiency. Examples include:

Predictive analytics: ML algorithms predict adverse events by analysing historical patient data, such as medical histories, genetic information, and treatment responses. This predictive capability enables early intervention, helping clinicians adjust protocols dynamically to mitigate risks and improve patient outcomes. For instance, adaptive trial modifications informed by ML have been shown to enhance trial safety and efficacy.

Table IV: Classification of clinical trial technologies into AI-powered and conventional tools*

Category	Tool Name	Function/Use	AI Integration
AI-Powered Tools	Deep6 AI	Patient recruitment from EHRs using NLP and ML	Yes
	4G Clinical	Uses NLP for randomisation and trial supply management	Yes
	Trials Home	AI-enabled decentralised and remote trial monitoring	Yes
	PathAI	Histopathological analysis using deep learning	Yes
	TriNetX	Uses AI for cohort discovery and real-world evidence generation	Yes
	Cytel's East	Supports adaptive trial design with ML models	Partial (AI-enhanced)
	Aris Global	Offers AI-enhanced pharmacovigilance and signal detection	Yes
	Veeva Vault with AI	Some Vault modules now include AI features for document control	Yes (in select modules)
Conventional Tools	Medidata CTMS, eTMF, Rave, Balance	Study management, EDC, RTSM, document management	No (Primarily rule-based)
	Oracle Siebel CTMS, Argus Safety	Trial and safety data management	No
	Veeva Vault CTMS, eTMF	Trial documentation and workflow management	No (unless AI module added)
	REDCap	Open-source EDC for academic trials	No
	OpenClinica	EDC and study data capture	No
	Epic & Cerner	EHR integration	No (but can feed AI tools)
	i2b2	Translational research platform	No (AI extensions possible)
	Almac	Randomisation and supply chain	No
	SAS, R, SPSS, Stata	Statistical analysis tools	No (R allows AI scripting)
	query, PASS	Sample size calculation	No
	Master Control, TrackWise	Regulatory and quality compliance	No
	Medrio ePRO, Clario eCOA	ePRO and patient diaries	No
	Bioconductor, Galaxy, SeqMonk	Genomic data analysis	No (AI possible via plugins)
	Tableau, Power BI, QlikView	Data visualisation tools	No (some AI add-ons possible)

* Integration of AI tools enhances patient recruitment, protocol optimisation, risk-based monitoring, and safety signal detection.

Recruitment optimisation: One of the most significant challenges in clinical trials is recruiting participants who meet specific eligibility criteria. ML models, such as those developed by Deep6 AI, leverage EHRs to identify suitable candidates swiftly. These algorithms analyse diverse variables including demographics, medical histories, and laboratory results to streamline recruitment. Studies indicate that such approaches can reduce recruitment time by up to 50%, ensuring trials progress without delays.

Natural Language Processing (NLP)

Natural Language Processing (NLP) transforms unstructured text data into actionable insights, addressing the complexities of analysing clinical notes, patient histories, and research articles. Key applications include:

Automating eligibility criteria extraction: NLP algorithms automate the extraction of inclusion and exclusion criteria from vast collections of medical records, reducing manual effort and errors. This capability ensures that trials enrol participants who precisely match the study's requirements, improving the reliability of results.

Sentiment analysis: By monitoring patient feedback in real-time, NLP tools analyse sentiment to gauge satisfaction, detect concerns, and improve engagement strategies. For example, sentiment analysis can identify patterns in patient responses to treatments, enabling researchers to address issues proactively and enhance retention rates.

Predictive algorithms

Predictive algorithms leverage historical and real-time data to optimise clinical trial parameters, providing actionable insights to enhance trial design and implementation. Examples include:

Dropout forecasting: High dropout rates pose significant risks to the validity of clinical trials. Predictive algorithms analyse behavioural, demographic, and medical data to identify participants at risk of discontinuing their involvement. By tailoring engagement strategies such as personalised communication and support researchers can improve retention rates, maintain data integrity and reducing costs.

Targeted therapy identification: Precision medicine relies on identifying patient subgroups most likely to benefit from specific

Table V: Real-world case studies of AI applications in clinical trials*

Case Study	AI Application	Key Outcomes	Organisation/Study
IBM Watson for Oncology	Patient-trial matching using NLP and ML	Improved recruitment speed and accuracy; faster matching from weeks to minutes	Memorial Sloan Kettering Cancer Center
Deep6 AI	Real-time patient recruitment from EHRs	Reduced recruitment time from 6 months to 2 weeks	Cedars-Sinai Medical Center
PathAI	Histopathology image analysis for trial endpoints	Improved diagnostic accuracy; reduced inter-observer variability	Bristol Myers Squibb
Trials@Home Initiative	Remote monitoring and adaptive trial management using AI	Increased adherence, decentralised access, and real-time monitoring	IMI – EU Public-Private Consortium

*Ethical and regulatory strategies are essential to ensure that AI integration in clinical trials remains transparent, patient-centric, secure, and fully compliant with evolving global standards for safety, privacy, and accountability.

treatments. Predictive algorithms integrate genetic, demographic, and clinical data to pinpoint optimal cohorts. This approach ensures therapies are administered to the right populations, enhancing efficacy and minimising adverse effects.^{21–23}

Case studies and transformative applications

AI in patient recruitment

Recruiting patients who meet specific eligibility criteria is often the most time-consuming and challenging phase of clinical trials. A study utilising Deep6 AI showcased significant advancements in recruitment efficiency by leveraging NLP to process vast amounts of unstructured data from EHRs. By identifying eligible patients based on detailed inclusion and exclusion criteria, Deep6 AI reduced recruitment timelines by 30%. Similarly, IBM Watson Health's AI platform expedited recruitment for oncology trials, effectively addressing delays caused by bottlenecks in patient enrolment. These platforms not only speed up the recruitment process but also enhance precision in matching patients to trials, improving data reliability and overall trial outcomes.

AI-driven adaptive trial designs

Traditional clinical trials follow fixed protocols, which may lead to inefficiencies when unanticipated events occur. In contrast, adaptive trials dynamically adjust parameters, such as dosage and sample size, based on real-time data. Medidata's AI solutions have been instrumental in implementing these adaptive designs, leading to reductions in trial durations by 20–30%. For example, during a phase III oncology trial, Medidata's AI monitored patient responses in real-time, enabling researchers to identify adverse effects early and modify trial parameters accordingly. This approach improves both safety and efficacy, allowing faster regulatory submissions and earlier access to innovative treatments for patients.

Predictive modelling in trial outcomes

Predictive algorithms play a crucial role in forecasting trial outcomes, enabling personalised medicine and reducing trial failures. Trials.ai, a leading AI-powered platform, integrates real-time patient data, including biomarkers, genetic information, and treatment responses, to predict outcomes with high accuracy. For instance, in a cardiovascular trial, Trials.ai identified optimal

dosing strategies by analysing historical and current patient data. This capability minimised adverse events and enhanced therapeutic efficacy. Furthermore, predictive models have been used to stratify patients into subgroups based on their likelihood of responding to specific therapies, ensuring more targeted and effective treatment protocols. By reducing uncertainties, these algorithms significantly improve trial success rates while optimising resources.^{24–26}

Regulatory and ethical challenges

Regulatory hurdles

The integration of AI into clinical trials necessitates compliance with evolving international regulatory frameworks. Notable challenges include:

Data Privacy: Regulations like the General Data Protection Regulation (GDPR) in the European Union and Health Insurance Portability and Accountability Act (HIPAA) in the United States impose strict requirements on the collection, storage, and processing of sensitive patient data. These laws mandate secure, de-identified data handling and define clear boundaries for cross-border data sharing.^{27–29}

Regulatory frameworks for AI in trials

The US FDA issued a discussion paper titled "Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning-Based Software as a Medical Device (SaMD)" that outlines a "total product lifecycle" approach for regulating AI in clinical settings. This encourages adaptive learning systems but requires rigorous validation at every step. The EU Artificial Intelligence Act (EU AI Act) proposes a risk-based framework, where AI used in clinical trials is categorised under "high-risk", demanding strict transparency, oversight, and conformity assessments before deployment. The ICH E6(R3) Guideline on Good Clinical Practice now also references the use of digital technologies including AI, promoting integrity, traceability, and participant protection throughout the trial process.

Algorithm transparency: Regulatory bodies increasingly expect explainability of AI algorithms. Clinical AI systems must not only be technically accurate but also interpretable to trial sponsors, investigators, and regulators. Explainable AI (XAI) approaches like SHAP (SHapley Additive explanations), LIME (Local Interpretable

Table VI: Ethical and regulatory strategies for responsible AI integration in clinical trials*		
Strategy	Description	Benefits
Explainable AI (XAI)	Use of interpretable models (e.g. LIME, SHAP) to clarify algorithm decisions	Enhances trust, supports regulatory approval
Bias Audits	Periodic evaluation of training datasets for demographic representativeness	Reduces health disparities
Algorithmic Traceability	Logging and version control of AI model updates and decisions	Supports reproducibility and validation
Ethical Review Boards	Specialised ethics committees reviewing AI integration in trials	Provides oversight on participant safety and rights
Participant Education	Development of clear consent forms that include AI use	Ensures informed, ethical participation

*Ethical and regulatory strategies ensure that AI in clinical trials remains transparent, patient-centric, secure, and compliant with evolving global standards for safety and accountability

Model-Agnostic Explanations)), and decision-tree models provide transparency into how outcomes are derived, supporting risk mitigation.

Ethical implications

AI introduces complex ethical challenges in the clinical trial landscape. Among the most pressing concerns are:

Bias in AI models

Case example: A 2019 study published in Science revealed that an AI healthcare algorithm used in US hospitals systematically underestimated the health needs of Black patients due to training on historical cost data rather than clinical need. This resulted in unequal access to clinical resources and highlights

how AI can perpetuate health disparities if trained on biased datasets. Such biases, if embedded into AI-driven recruitment or diagnostic algorithms in clinical trials, can lead to exclusion of underrepresented groups, affecting trial generalisability and patient safety.

Informed consent in AI trials

Traditional informed consent processes often overlook the involvement of AI in data analysis or decision-making. Ethical guidelines now urge for “algorithmic disclosure”, where trial participants are explicitly informed about the role of AI, its decision-making functions, data usage, and potential limitations. This is aligned with ethical principles laid out by the World Medical Association (WMA) Declaration of Helsinki, emphasising transparency and autonomy in clinical research.^{30,31}

Table VII: Comparison of traditional method and AI-driven methods in clinical research*		
Feature	Traditional Methods	AI-Driven Methods
Data Analysis	Primarily relies on manual analysis and statistical methods, which can be time-consuming and prone to errors	Leverages machine learning algorithms to identify patterns, correlations, and potential drug candidates faster and more accurately
Patient Recruitment	Relies on manual patient matching and screening, which can be inefficient and time-consuming	Uses AI algorithms to analyse patient databases and identify suitable candidates more efficiently, potentially accelerating trial timelines
Patient Monitoring	Typically relies on periodic manual checks, which may not provide a comprehensive view of the patient's condition and can lead to delayed detection of adverse events	Enables real-time monitoring using wearable devices and sensors, allowing for early detection of potential issues and proactive intervention
Trial Design	Requires extensive human input and experience in designing and optimising protocols	Can automate certain aspects of trial design, such as identifying optimal dosages and study duration, potentially reducing costs and time
Accuracy and Reliability	While traditional methods are reliable, they can be subjective and may be influenced by human error	AI algorithms can be highly accurate and objective, reducing the risk of human bias
Predictive Modelling	Traditional methods may rely on simple models or historical data, limiting their predictive power	AI can develop sophisticated predictive models that can forecast patient outcomes, drug efficacy, and potential safety issues
Cost	Traditional clinical trials can be expensive and time-consuming, particularly for large-scale studies	AI can potentially reduce costs and time by automating tasks and improving efficiency, leading to faster drug development
Ethical Considerations	Requires careful consideration of ethical implications, such as patient privacy and data security	Raises similar ethical considerations, particularly regarding algorithmic bias and data privacy, requiring careful implementation and oversight
Expertise Required	Requires extensive training and experience in clinical trials and statistical analysis	Requires specialised expertise in AI, machine learning, and data analysis, alongside traditional clinical knowledge
Interpretability	Traditional methods are generally more interpretable and explainable to stakeholders	AI models can be less interpretable, requiring careful interpretation and explanation to ensure transparency and trust

* AI-driven methods in clinical research offer faster, more data-efficient, and predictive decision-making compared to traditional approaches that rely on manual, time-consuming processes.

Comparative analysis: AI vs. traditional methods

Efficiency

Traditional methods often encounter delays due to manual processes in data collection and analysis. In contrast, AI automates these processes, significantly reducing trial timelines and operational costs.

Accuracy

Traditional trials rely on limited datasets, which can introduce errors. AI's ability to process vast amounts of data ensures more accurate predictions and reliable outcomes.

Scalability

AI tools are inherently scalable, making them suitable for managing multi-site and global trials, thus broadening their applicability in diverse clinical settings.

Risk mitigation strategies: To ensure safe and compliant AI adoption in clinical trials, the following strategies are recommended:

Data security

Implement robust encryption protocols and access controls to protect patient data. Utilise decentralised storage systems to reduce risks associated with centralised data breaches.

Bias mitigation

Train AI models on diverse and representative datasets to minimise bias. Regularly validate models across different populations and geographies to ensure fairness in outcomes.

Continuous monitoring

Conduct regular audits of AI tools to detect and rectify errors or biases. Implement real-time monitoring systems to track AI performance and identify anomalies promptly. Adaptive mechanisms should be in place to adjust algorithms as needed.^{32–35}

Advantages and limitations of AI in clinical trials

Sl. No.	Advantages of AI in Clinical Trials	Limitations of AI in Clinical Trials
1	Faster patient recruitment using EHR data	Dependence on high-quality and complete data
2	Improved accuracy in data analysis	Risk of algorithmic bias
3	Predictive modelling for outcomes and ADR detection	Lack of transparency (black-box models)
4	Reduction in cost and trial duration	High implementation and maintenance cost
5	Real-time patient monitoring using wearable devices	Data privacy and security concerns
6	Enhanced and adaptive clinical trial design	Regulatory uncertainty and lack of global standards
7	Better patient stratification and personalised treatment	Requirement of skilled professionals and technical expertise
8	Automation of repetitive tasks	Ethical concerns (consent, autonomy, AI decision-making)

Future perspectives and novel contributions

Although AI has demonstrated significant potential in improving clinical trials, its full impact will depend on effective integration with real-world healthcare systems and regulatory frameworks. Future advancements are expected to focus on the use of real-world data, digital health platforms, and decentralised clinical trial models to enable continuous and patient-centric research. The development of explainable and transparent AI models will be essential to enhance trust among clinicians, researchers, and regulatory authorities. In addition, AI-driven adaptive and personalised trial designs have the potential to improve treatment outcomes by tailoring interventions based on patient-specific characteristics.

Despite these advancements, challenges such as data standardisation, interoperability, ethical concerns, and regulatory uncertainty must be addressed to ensure safe and effective implementation. Global harmonisation of AI-related guidelines will play a crucial role in enabling broader adoption. This review contributes by integrating AI techniques, software tools, practical applications, and regulatory challenges into a single comprehensive framework. It also highlights future directions that emphasise the need for a balanced approach combining innovation with safety, transparency, and compliance in clinical research.

Conclusion

The application of AI in clinical trials is a big step forward, changing medical research and pharmaceutical development. Clinical trials have traditionally been hindered by long recruiting delays, high costs, and sophisticated data analysis requirements. Early software solutions helped manage trial data, but lacked the predictive capability and agility required for real-time decision-making. AI, on the other hand, brings a new level of capabilities, allowing for the quick analysis of enormous datasets, flexible trial designs, and precise predictions of patient reactions. AI-powered solutions speed up all aspects of clinical trials, from patient recruiting to real-time monitoring, resulting in lower costs and increased trial safety and efficacy. Predictive algorithms can swiftly identify proper candidates and follow patient reactions, boosting the likelihood of favourable outcomes. AI is boosting drug development efficiency and accessibility by rethinking the trial process as well as enhancing existing approaches. As AI technology progresses, it is poised to overcome long-standing obstacles, setting a new standard for clinical research and speeding the availability of transformational therapeutics for patients globally.

Conflicts of interest

There are no conflicts of interest.

Novelty statement

AI in clinical trials accelerates patient recruitment, refines data analysis, and enhances safety. This transformative approach reduces costs and time, bringing innovative therapies to patients faster than ever before.

Declaration of generative AI

During the preparation of this work, the authors Gaganashree TV, Chinmayee U Gowda, and Balamuralidhara V used ChatGPT to assist with idea generation, drafting, language refinement. After using this tool, the authors thoroughly reviewed and edited the content as needed, assuming full responsibility for the final publication.

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Barriers to the utilisation of pharmacogenetic testing for warfarin patients in South Africa

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Abstract

Background: Despite its narrow therapeutic index and variable response, warfarin remains a widely used first-line anticoagulant in South Africa. Although pharmacogenetic testing may improve dosing accuracy and treatment outcomes, implementation in community pharmacy practice is limited.

Aim: To examine barriers to pharmacogenetic testing for warfarin in community pharmacies, assess pharmacists' knowledge and awareness, explore attitudes, and propose strategies for implementation.

Methods: A national cross-sectional survey of pharmacists examined knowledge and awareness, attitudes and perceptions, current practices and perceived barriers. Quantitative data were analysed descriptively and inferentially; qualitative responses underwent thematic analysis.

Results: Following application of exclusion criteria, 162 pharmacists participated. Most demonstrated strong basic knowledge of warfarin pharmacology, but confidence in dose adjustments based on international normalised ratio (INR) ranges and pharmacogenetic testing was weaker. Awareness of pharmacogenetics was high, yet fewer than 60% understood how to apply results in practice. Attitudes were positive, with 98% recognising that pharmacogenetics could improve outcomes. Barriers included limited training (77%), lack of guidelines (82%), high costs (72%), and restricted access to INR data. Qualitative themes highlighted professional enthusiasm, tempered by concerns over feasibility, scope of practice, and patient acceptance. Mapping to the Capability, Opportunity, Motivation - Behaviour model and Theoretical Domains Framework revealed high motivation but gaps in capability and opportunity, underscoring the need for education, supportive infrastructure, and policy alignment.

Conclusion: South African pharmacists recognise the potential of PGx for warfarin but face systemic, economic, and educational barriers. Addressing these through training, guidelines, reimbursement, and interprofessional collaboration is critical for sustainable implementation.

Keywords: pharmacogenetics, warfarin, pharmacists, South Africa, implementation

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Introduction

Warfarin remains a cornerstone of anticoagulation therapy in South Africa. Although direct oral anticoagulants (DOACs) are available, their use may be constrained by cost, access, and clinical eligibility criteria. Atrial fibrillation is a common indication for warfarin use in local healthcare facilities.¹

Safe and effective use of warfarin is complicated by inter-patient variability in dose requirements and a narrow therapeutic window, increasing the risk of bleeding or thrombosis.¹ Genetic variability, particularly in the expression of the cytochrome P450 family 2 subfamily C polypeptide 9 (CYP2C9) and vitamin K epoxide reductase complex subunit 1 (VKORC1) enzymes, influences warfarin response, as depicted in Figure 1.² International guidelines therefore recommend pharmacogenetic (PGx) testing to support safe initiation and dose titration.³

South Africa faces unique challenges in integrating PGx into practice.⁴ Community pharmacists, given their accessibility and medicines expertise, are ideally positioned to advance the

implementation of precision medicine, yet their role in PGx testing remains underexplored.⁵

This study aimed to describe barriers to the utilisation of PGx testing for warfarin patients in South African community pharmacies, while also evaluating pharmacists' knowledge, awareness, attitudes, perceptions and current practices, and proposing strategies to support its integration into practice. Findings were also mapped to the Theoretical Domains Framework (TDF) and the Capability, Opportunity, Motivation-Behaviour (COM-B) model to contextualise behavioural determinants influencing implementation.

Methods

A national cross-sectional survey of South African community pharmacists was conducted using a self-administered questionnaire. Items covered demographics, warfarin knowledge, PGx awareness and understanding, attitudes, current practices, and perceived barriers. Practice setting was self-reported and categorised as either chain pharmacy franchise or private

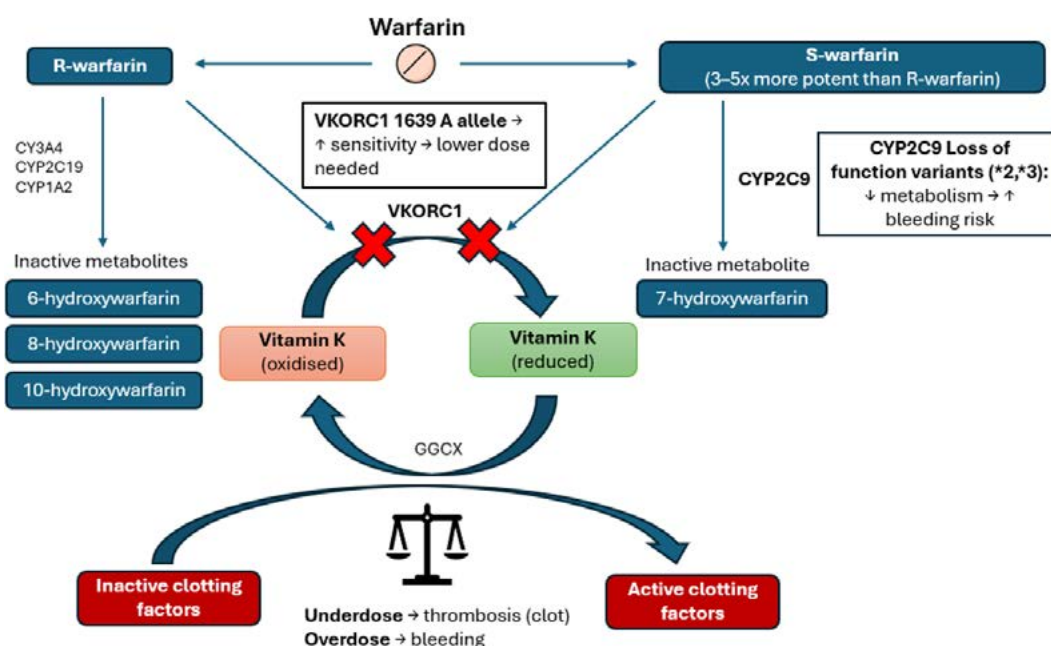


Figure 1: Pharmacogenetic and metabolic pathways of warfarin

independent pharmacy. Chain pharmacies were defined as corporate or franchised pharmacy groups operating multiple branches under a shared brand, while independent pharmacies referred to privately owned community pharmacies. The survey was distributed electronically via email using a professional contact database and through pharmacy networks and social platforms. As the database did not differentiate between practice sectors and the survey link was shareable, the exact number of eligible community pharmacists reached could not be determined. Responses from pharmacists outside the community sector were excluded prior to analysis. The questionnaire included dichotomous, Likert-type and open-ended questions.

Likert-type responses were categorised as positive (strongly agree/somewhat agree) versus non-positive (neutral/disagree/strongly disagree). Respondent characteristics and responses were summarised using descriptive statistics. Differences by qualification and experience were assessed using χ^2 tests, Fisher's exact test, or the Wilcoxon rank-sum (Mann-Whitney) test, as appropriate. Composite scores were created for basic warfarin knowledge, advanced clinical application, and PGx familiarity. Associations between knowledge and attitudes or practices were examined with odds ratios and 95% confidence intervals. Free-text responses were analysed inductively to identify themes. Relevant findings were mapped to the Theoretical Domains Framework (TDF), a behavioural framework used to identify determinants of practice, and considered within the COM-B model to explore factors influencing PGx implementation in community pharmacy practice.

Ethical approval was obtained from the Human and Social Sciences Research Ethics Committee (HSSREC) at the University of KwaZulu-Natal (HSSREC/00005574/2023). Informed consent was obtained electronically from all participants and confidentiality was assured.

Table 1: Respondents' demographic characteristics ($n = 162$)

Characteristics	Frequency ($n = 162$)	Percentage (%)
Sex		
Female	90	55.6%
Male	69	42.6%
Prefer not to indicate	3	1.9%
Age		
20–30 years	41	25.3%
31–40 years	51	31.5%
41–50 years	25	15.4%
51–60 years	26	16.1%
> 60 years	19	11.7%
Highest qualification		
BPharm	129	79.6%
MPharm/MSc	23	14.2%
Doctorate/PhD	5	3.1%
Other (Primary Care Drug Therapy (PCDT), diploma, short course qualification)	5	3.1%
Community pharmacy setting		
Chain pharmacy	84	51.9%
Independent pharmacy	71	43.8%
Other (compounding or integrated health community practices)	7	4.3%
Years of experience as a community pharmacist		
≤ 5 years	32	19.8%
5–10 years	44	27.2%
10–15 years	26	16.1%
> 15 years	60	37.0%

Results

Demographics

A total of 233 pharmacists responded to the survey. Following the application of exclusion criteria, 162 eligible community pharmacists were included in the final analysis. Most were female (90; 55.6%) and aged 31–40 years (51; 31.5%). The majority held a BPharm degree as their highest qualification (129; 79.6%), with a minority reporting postgraduate qualifications (33; 17.3%). Just over half worked in chain pharmacies (84; 51.9%). Experience was broadly balanced, with 76 (47.0%) having spent 10 years or less in practice. The respondents' demographic characteristics are shown in Table I.

No significant associations were observed between demographic characteristics and practice setting, qualification, or experience. More pharmacists practising in chain pharmacies had only 5–10 years' experience (27; 32.1%), whereas a larger proportion of pharmacists with more than 15 years' experience worked in independent pharmacies (32; 45.1%). A higher proportion of female pharmacists (21; 23.3%) than males (9; 13.0%) had five or less years' experience. By contrast, men were more represented in the group with 5–10 years' experience (25; 36.2% vs. 18; 20.0%).

Knowledge and awareness

Most respondents reported knowledge of warfarin's indications (139; 85.8%) and understanding of INR terminology (152; 94.4%), though fewer could identify target INR ranges (77; 47.5%) or determine appropriate dose adjustments (84; 51.9%), as shown in Figure 2. Composite scoring confirmed that stronger basic knowledge was significantly associated with advanced application, i.e., being able to interpret INR values and propose dose adjustments ($p < 0.001$).

Awareness of PGx was high (124; 76.5%), but fewer (89; 55.3%) understood how to use such test results.

Postgraduates were more likely than BPharm-only pharmacists to report PGx awareness (96.4% vs. 72.4%, $p = 0.006$) and understanding (82.1% vs. 49.3%, $p = 0.002$). Similarly, those with 10 years or less experience reported greater awareness (84.2% vs. 69.8%, $p = 0.030$) and understanding (63.2% vs. 47.7%, $p = 0.048$). Composite scores confirmed these trends. 82.1% of postgraduates and 63.2% of less-experienced pharmacists achieved the highest familiarity score, compared with 47.8% of BPharm-only and 45.3% of more experienced respondents.

Attitudes and perceptions

Pharmacists expressed strong support for PGx. Almost all believed it could improve patient outcomes (159; 98.2%) and benefit patients directly (154; 95.1%), while 85.8% felt rapid INR testing could support implementation. Most agreed PGx has a place in community pharmacy (144; 88.9%) and 79.6% were comfortable offering testing, although fewer (119; 73.5%) were confident on dose adjustments.

Perceived value was high. 92.6% believed PGx would improve medicine-related outcomes, 90.1% it would enhance pharmaceutical care, and 70.4% that it could strengthen pharmacist-doctor collaboration. Long-term healthcare cost savings were anticipated by 80.3% of respondents.

Concerns centred on competence and resources. Only 61.7% felt they had the skills to interpret PGx results within the context of medication management and 56.2% felt competent to provide related services. Time (46; 45.0%) and funding (73; 45.1%) were common barriers, while ethical concerns were minimal, with 85.2% disagreeing that PGx testing is unethical.

Comparisons showed broadly similar attitudes across subgroups. Postgraduates were slightly less likely than BPharm-only pharmacists to report comfort with PGx implementation (71.4% vs. 81.3%) and involvement in dose optimisation decisions (64.3% vs. 75.4%). These differences were not significant. Pharmacists

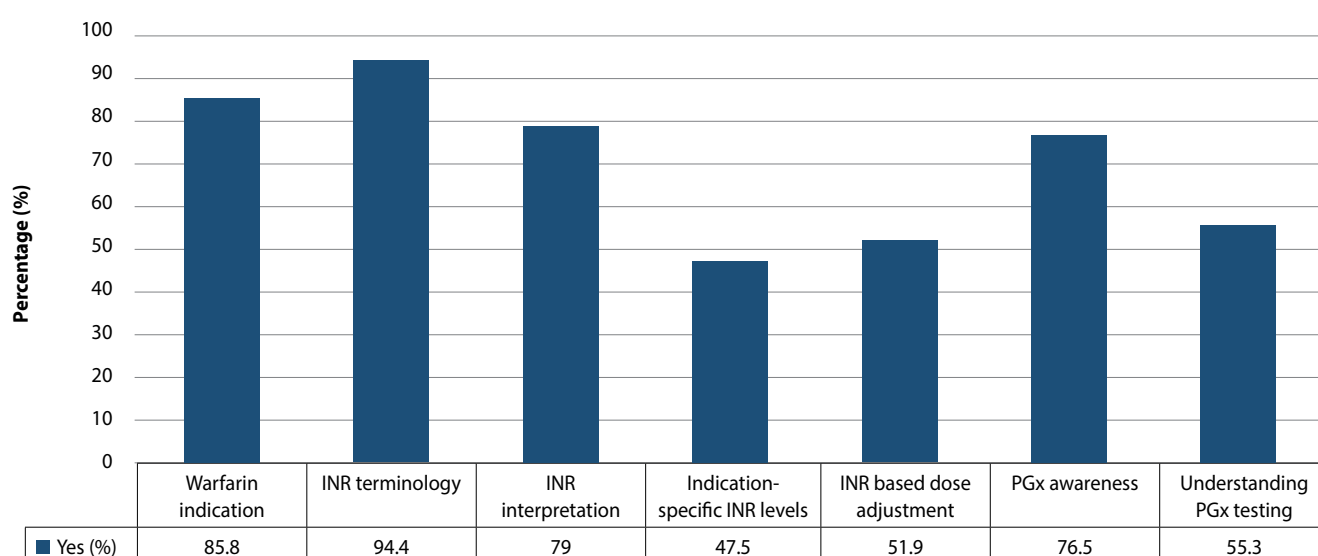


Figure 2: Proportion of pharmacists reporting knowledge of warfarin therapy and pharmacogenetics ($n = 162$)

with 10 years or less experience were more likely to report PGx knowledge (69.7% vs. 54.7%, $p = 0.049$).

Familiarity with PGx was strongly associated with greater competence (67.4% vs. 42.5%, $p = 0.001$; OR 2.8), confidence in applying pharmacogenetic information within medication management (66.1% vs. 47.4%, $p = 0.040$; OR 2.2), and comfort contributing to dose optimisation with prescribers (79.8% vs. 65.8%, $p = 0.040$; OR 2.05).

Current practices

Most pharmacists (119; 73.5%) reported no access to INR values, and INR results were rarely included on prescriptions (111; 68.5%). By contrast, 90.1% (146) believed INR values should routinely be included on prescriptions. Point-of-care INR testing was almost absent (2; 1.2%).

When faced with dose changes, 70.4% (114) engaged patients and 16.7% (27) contacted prescribers, while 11.1% (18) accepted changes without question. Information requests varied. 21.0% (34) asked for the INR, 7.4% (12) for indication, 30.3% (49) for both, and 37.0% (60) requested no additional information.

Almost half (74; 45.7%) had made a warfarin-related intervention, but only 26.5% (43) documented these. More than half (91; 56.2%) reported frequent patient complaints of warfarin side effects.

Collaboration with prescribers was limited, 39.5% (64) had advised doctors on dosing, while 59.9% (97) had referred patients back to prescribers.

By subgroup, pharmacists with 10 years or less experience were more likely than those with more than 10 years to question dose changes (93.4% vs. 81.4%, $p = 0.010$). Knowledge of warfarin dose adjustment was also linked to practice, with pharmacists reporting confidence in adjusting warfarin dosing when INR results were available being more likely to query warfarin prescription changes ($p = 0.002$).

Table II provides the full distribution of responses across attitudes, perceptions, and current practice items.

Barriers to implementation

Pharmacists reported multiple barriers to implementation (Figure 3). For reporting purposes, individual items were grouped into four broad categories – organisational, professional, resource-related, and socio-cultural. Organisational barriers included limited management support (86; 53.1%), poor organisational climate (73; 45.1%), and lack of rapid INR testing (84; 51.9%); legislative issues were less commonly cited (47; 29.0%).

Professional barriers included doctor acceptance (91; 56.2%), communication challenges (60; 37.0%), language barriers (66; 40.7%), training gaps (125; 77.2%) and absence of guidelines (132; 81.5%), with the latter two being most frequently reported.

Resource-related barriers were the most prominent barriers overall such as a lack of compensation (128; 79.0%), high testing costs (116; 71.6%), and patient affordability (132; 81.5%).

Table II: Attitudes, perceptions and current practices surrounding warfarin management and PGx among community pharmacists ($n = 162$)

Attitudes and perceptions	Frequency ($n = 162$)	% Agreement
PGx can improve patient outcomes	159	98.2
Patients would benefit from PGx	154	95.1
Rapid INR testing supports PGx	139	85.8
Comfortable implementing PGx in pharmacy	129	79.6
Comfortable adjusting doses with PGx results	119	73.5
PGx testing could yield cost savings	130	80.3
PGx improves medicine-related outcomes	150	92.6
PGx improves value of pharmaceutical care	146	90.1
PGx strengthens pharmacist-doctor collaboration	114	70.4
Pharmacists have skills to interpret PGx results	100	61.7
Pharmacists competent to provide PGx services	91	56.2
Do not have time to implement	73	45.0
Pharmacy does not have funding to implement	73	45.1
Patients complain of warfarin related side effects	85	52.4
Pharmacist knowledge and skill to make drug related interventions	137	84.6
Comfort intervening on incorrect doses	147	90.8
Role of pharmacist to counsel on DNA impact on medicine	129	79.6
PGx has a space within community pharmacy	144	88.9
PGx testing unethical	5	3.1
Current Practices	Frequency ($n = 162$)	% Agreement
Access to patients' INR values	30	18.5
Offer rapid INR testing in pharmacy	2	1.2
Prescribers include INR on scripts	8	4.9
Believe INR should be on scripts	146	90.1
Question warfarin dose changes (patient/doctor)	141	87.1
Request INR + indication before dispensing	49	30.3
Have made a warfarin-related intervention	74	45.7
Document interventions	43	26.5
Advised doctors on warfarin dosing	64	39.5
Referred patients back to prescriber	97	59.9

Socio-cultural barriers were less frequent, with 56.2% (91) citing patient acceptance of new technology, 15.4% (25) reporting cultural or religious concerns, and only 3.7% (6) citing their own beliefs.

No significant differences were observed by experience, qualification, or practice setting. Training gaps and absence of guidelines were strongly associated ($p < 0.001$).

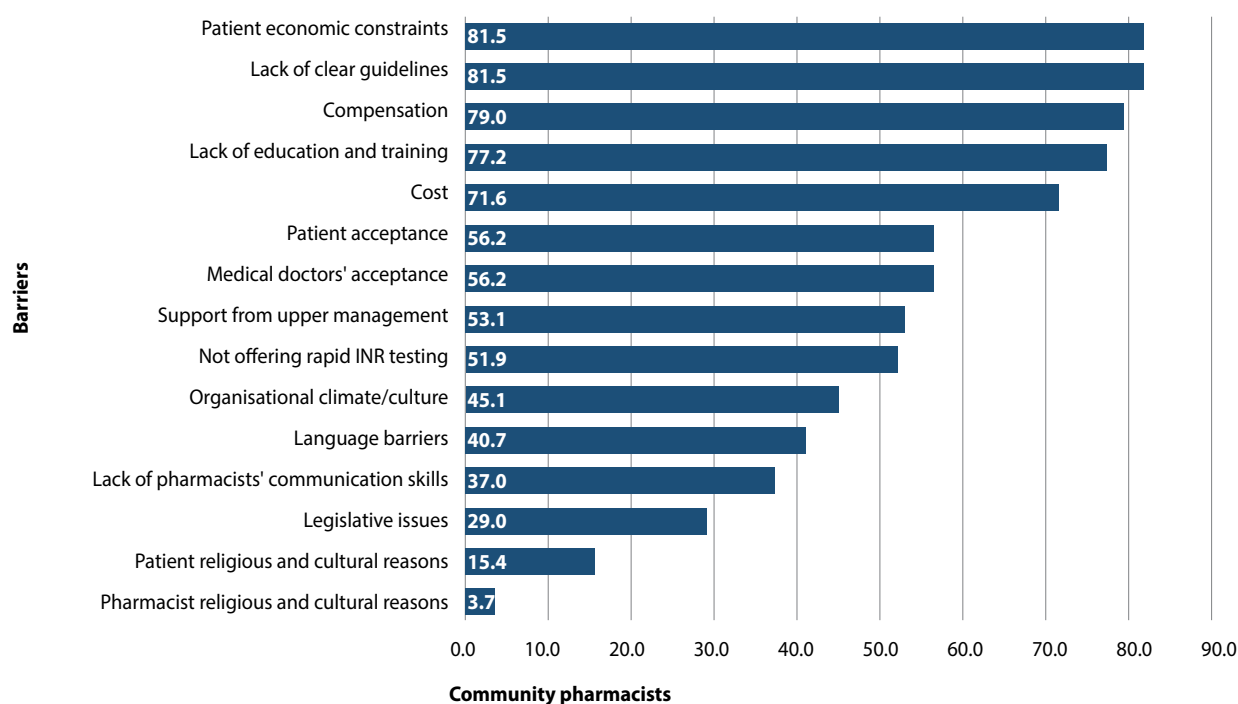


Figure 3: PGx in warfarin: barriers perceived by South African pharmacists

Qualitative findings

Open-ended feedback was provided by 84.6% of respondents. Thematic analysis identified three themes: professional enthusiasm and perceived benefits, implementation concerns, and practical feasibility.

Professional enthusiasm

Pharmacists expressed optimism about PGx, noting its potential to improve outcomes, enhance safety through personalised dosing, and expand their clinical role. Many highlighted opportunities for closer collaboration with doctors and alignment with outcomes-based care. One participant remarked, *"Pharmacogenetic testing will greatly benefit patients on warfarin and could potentially save lives and reduce complications due to incorrect dosing."* Another added, *"It will add value to the provision of outcomes-based pharmaceutical care."*

Implementation concerns

Barriers included resistance from doctors, gaps in pharmacist training, and lack of clear guidelines. Respondents emphasised the need for education, protocols, and interprofessional alignment before adoption. As one pharmacist noted, *"Success depends on all healthcare providers being on the same page and offering advice which is consistent and non-conflicting."* Another commented, *"Pharmacists have the knowledge and skill to perform pharmacogenetic testing and interpret the results but require additional education and training."*

Practical feasibility

Cost was the dominant concern, both for patients and pharmacies, compounded by lack of reimbursement, courier fees, and

workflow challenges. Some questioned PGx relevance for warfarin given declining use, suggesting greater value in other therapeutic areas. One participant expressed, *"If cost factors can be mitigated through medical aid or government support, I feel pharmacogenetics has a place in the future of healthcare."*

Overall, pharmacists were supportive of PGx. Open-ended responses reflected similar themes, with participants frequently citing the need for training, clear guidelines, collaboration with prescribers, and financial feasibility to support implementation.

Behavioural framework mapping

Relevant findings were mapped to the TDF domains to contextualise factors influencing PGx implementation (Table III). Findings were further interpreted within the broader COM-B model in the discussion.

Discussion

This study explored South African community pharmacists' knowledge, attitudes, current practices, and perceived barriers toward PGx testing for warfarin management. To our knowledge, it represents the first national survey of pharmacists' readiness to adopt PGx in this therapeutic area. Findings demonstrate strong enthusiasm for PGx integration, but highlight persistent gaps in knowledge, systemic constraints, and concerns about feasibility.

Pharmacists showed strong basic knowledge of warfarin therapy, particularly its indications and INR monitoring. Advanced application, such as interpretation of target INR values and contributing to dose optimisation decisions, was weaker. Awareness of PGx was relatively high, yet fewer than 60% reported understanding how to apply PGx results in practice.

Similar trends have been documented internationally, where pharmacists report moderate awareness but limited confidence in clinical use.⁶⁻⁹ This reflects a theory-practice gap, echoing Latif.¹⁰ Locally, Sonuga et al.¹¹ highlighted similar challenges in warfarin management, particularly in atrial fibrillation care. Importantly, this study found a significant association between higher basic knowledge and greater confidence in advanced application, highlighting the need to strengthen foundational competence as a gateway to PGx-informed clinical use.

Attitudes toward PGx implementation were positive. Over 90% agreed that PGx can improve patient and medicine-related outcomes, enhance the value of pharmaceutical care, and that patients would benefit from testing. Close to 90% agreed that PGx has a place within community pharmacy. However, fewer than two-thirds felt confident in their ability to interpret PGx results or provide services. This pattern, where enthusiasm outpaces readiness, mirrors findings from other countries.^{12,13} African studies similarly highlight optimism alongside systemic training and infrastructure gaps.¹⁴

Current practices revealed structural limitations in routine warfarin management. Most pharmacists lacked access to INR results, as INR values were rarely recorded on prescriptions, and point-of-care

testing was almost entirely absent. These constraints restricted pharmacists' ability to verify dosing or make evidence-based interventions. Nevertheless, many reported counselling patients or referring them back to prescribers, reflecting professional willingness to engage despite limited resources. Similar fragmentation has been described internationally, where poor access to clinical data undermines pharmacists' contributions.^{15,16} In South Africa, the continued reliance on warfarin makes these challenges especially pressing.

Barriers reported in this study were largely systemic and not tied to specific demographic or practice-related subgroups. Resource-related barriers were most prominent, while professional barriers centred on training gaps and the absence of guidelines. Organisational and socio-cultural barriers were cited less frequently. These findings are consistent with global literature identifying cost, reimbursement, and education as barriers to PGx adoption.^{5,17,18} Equity concerns, particularly affordability and patient access, have also been emphasised in African genomics literature, highlighting risks of widening health disparities.¹⁴ In South Africa, weak regulatory frameworks and limited health-system integration have further constrained PGx development.^{19,20}

Table III: Study findings mapped to TDF domains

TDF Domain	Study Findings	Interpretation
Knowledge	Pharmacists showed strong baseline warfarin knowledge, but PGx-specific knowledge (e.g., target INR ranges, PGx-guided dose adjustments) was uneven.	Knowledge gaps highlight the need for structured CPD and inclusion of PGx in curricula.
Skills	Only ~52% felt confident adjusting warfarin doses based on INR; fewer could apply PGx in practice.	Indicates limited hands-on skills and insufficient practical training opportunities.
Social/professional role and identity	Pharmacists saw PGx as part of their professional role but reported unclear role boundaries with doctors.	Role ambiguity undermines interprofessional collaboration and limits pharmacists' ability to act.
Beliefs about capabilities	Confidence was low in applying advanced PGx knowledge, even when awareness was present.	Lack of self-efficacy reduces readiness for implementation despite positive attitudes.
Optimism	Many pharmacists described PGx as a "life-saving intervention" and an extension of their clinical role.	Optimism reflects motivation and openness to innovation if systemic barriers are addressed.
Beliefs about consequences	Broad agreement that PGx would improve patient outcomes, reduce ADRs, and support safer dosing.	Pharmacists recognise clinical value, strengthening case for integration.
Reinforcement	Lack of reimbursement and compensation cited as major barriers.	Without financial recognition, behaviour change is unlikely to be sustained.
Intentions	Pharmacists expressed willingness to adopt PGx if training, guidelines, and support were available.	Positive intentions suggest readiness to act once enabling structures are in place.
Goals	Pharmacists indicated that PGx aligns with professional goals of advancing patient safety and personalised care.	Suggests good strategic fit, but systemic barriers prevent translation into practice.
Memory, attention, and decision processes	Time and workload pressures made PGx a lower priority in busy pharmacy settings.	Competing demands crowd out new practices unless workflows are redesigned.
Environmental context and resources	Dominant barrier: lack of compensation, patient affordability, absence of INR testing, insufficient infrastructure, unsupportive management, policy gaps.	Confirms that systemic and resource-related barriers, not attitudes, are the biggest obstacles.
Social influences	Over half cited lack of doctor acceptance as a barrier; communication and language barriers also noted.	Peer and prescriber influence strongly shape adoption potential.
Emotion	Some pharmacists reported anxiety/uncertainty about applying PGx without training or guidelines.	Emotional factors (uncertainty, lack of confidence) reinforce practical barriers.
Behavioural regulation	Absence of protocols and decision-support tools; pharmacists requested guidelines and checklists.	Without behavioural regulation mechanisms, practice remains inconsistent and hesitant.

A strong association between training gaps and absence of guidelines was found, emphasising the interdependence of educational and structural enablers. Resource-related barriers often co-existed with professional and organisational challenges, reflecting their systemic nature.

Qualitative responses reinforced these patterns. Pharmacists described PGx as promising, but consistently linked their confidence to training, protocols, and collaboration with prescribers. Concerns included professional resistance from doctors, affordability, logistical challenges, and the declining use of warfarin in favour of newer anticoagulants. While enthusiasm was strong, responses reflected caution, shaped by both systemic limitations and perceptions of feasibility.

Interpreted through the COM-B model,²¹ the findings indicate strong motivational support for PGx implementation, alongside capability and opportunity constraints. While pharmacists expressed positive attitudes toward PGx, confidence in applying results was lower, and barriers centred on access to INR data, clear guidelines, and reimbursement structure. Within the TDF,²² implementation barriers appeared largely shaped by environmental and systemic factors rather than negative attitudes. The most relevant domains were knowledge, skills, environmental context and resources, and social/professional role and identity. These domains highlight where targeted interventions – such as PGx education, national guidelines, and supportive infrastructure – could bridge the gap between enthusiasm and practical implementation (Table III).

Ultimately, this study demonstrates that South African community pharmacists show strong motivation and positive perceptions toward the integration of pharmacogenetic testing, although systemic and capability-related barriers remain. With appropriate structural support, PGx implementation in community pharmacy appears feasible.

Implications

Community pharmacists are accessible frontline healthcare providers and are well-positioned to play a meaningful role in precision medicine. However, integration of PGx into practice will require:

1. embedding PGx education into undergraduate curricula and continuing professional development;
2. developing national guidelines, decision-support tools, and protocols;
3. establishing reimbursement pathways to ensure affordable access; and
4. strengthening collaborative frameworks with prescribers to promote interprofessional trust.

Limitations

The study relied on self-reported data, which may introduce bias. Its cross-sectional design precludes causal inference, and the sample represents a proportion of the national community

pharmacist population. Geographic distribution was not captured, limiting assessment of regional representativeness. Generalisability may therefore be constrained. Nonetheless, the survey provides valuable quantitative and qualitative insight into pharmacists' perceptions of warfarin PGx implementation. In conclusion, South African pharmacists are motivated to adopt PGx testing for warfarin but face significant educational, systemic, and economic barriers. Addressing these requires coordinated action across education, policy, and practice to enable pharmacists to contribute meaningfully to the implementation of precision medicine.

Conflict of interest

The authors declare no conflict of interest.

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Ethical approval

Ethical clearance for the study was obtained from the Humanities and Social Sciences Research Ethics Committee (HSSREC) of the University of KwaZulu-Natal (Protocol reference number: HSSREC/00005574/2023).

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Prediabetes as the reversible window: academic reflections on a breakfast symposium at SEMDSA Congress 2026

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Abstract

At the 58th Annual Congress of the Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA), a breakfast symposium delivered by Professor Peter E. H. Schwarz revisited prediabetes as a biologically active and potentially reversible stage in the trajectory towards type 2 diabetes. This opinion paper reflects on the symposium through three deliberately signposted questions: why prediabetes matters, what may still be reversible, and how clinicians and health systems can act in practice. The central message - that prediabetes should prompt active pursuit of normoglycaemia rather than passive risk recognition - aligns with evidence supporting structured lifestyle intervention, regression from prediabetes to normal glucose regulation, and selective metformin use in high-risk individuals.¹⁻⁴ The paper also considers environmental determinants, including air pollution, and uses a South African clinical vignette and practical box to translate the lecture's scientific themes into non-promotional, patient-centred prevention steps. For South African practice, the symposium's value lies in reframing prediabetes as a reversible clinical opportunity that requires structured prevention pathways, patient-centred communication, careful risk stratification, and system-level support.

Keywords: Prediabetes, remission, diabetes prevention, lifestyle intervention, metformin

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Introduction

Professor Peter E. H. Schwarz, President of the International Diabetes Federation (IDF), presented the Merck Breakfast Symposium entitled "Prediabetes: The Reversible Window" on 17 April 2026 during the 58th SEMDSA Congress in Cape Town. Figure 1 shows Professor Schwarz delivering the symposium.

This reflection is organised around three practice-facing questions: why prediabetes matters, what may still be reversible, and how South African clinicians and health systems can act.

At its core, the session repositioned prediabetes as a clinically meaningful and potentially reversible condition, rather than a vague precursor of future disease. This matters because prediabetes is often diagnosed but not always acted on with sufficient intensity. The lecture proposed restoration of normoglycaemia as a realistic treatment goal and encouraged earlier, more deliberate intervention within the reversible window.¹

Why prediabetes matters

The prevention window is epidemiologically important. Global estimates project substantial increases in both impaired glucose tolerance (IGT) and impaired fasting glucose (IFG), while the IDF Diabetes Atlas 11th edition estimates that 589 million adults aged 20-79 years were living with diabetes in 2024, with a projected rise to 853 million by 2050.^{5,6} Approximately 252 million adults with diabetes were estimated to be undiagnosed in 2024, underscoring the importance of earlier detection and prevention.⁶ For South African clinicians, this global picture is not abstract: it intersects with a local non-communicable disease (NCD) burden in which



Figure 1: Professor Peter E. H. Schwarz presenting "Prediabetes: The Reversible Window" at the Merck Breakfast Symposium, SEMDSA Congress 2026, Cape Town, 17 April 2026. Photograph supplied by the author.

earlier detection, risk stratification and prevention are central health-system priorities.^{18,19}

Prediabetes matters because it is not merely a laboratory label. It finds a point on the dysglycaemic continuum where insulin resistance, β -cell stress, visceral adiposity, hepatic fat accumulation, and cardiovascular risk may already be present, but where the trajectory may still be altered. The term "reversible window" is therefore clinically useful if it changes behaviour: it should prompt structured intervention, planned review, and an explicit attempt to move the person back towards normal glucose regulation, rather than simply documenting risk.

The South African relevance of this message lies in its pragmatism. A clinician in a busy primary-care or private-practice setting does not need to turn every person with prediabetes into a specialist referral. However, the diagnosis should trigger a prevention pathway: confirm dysglycaemia, assess overall cardiometabolic risk, communicate hope without minimising risk, start structured lifestyle support, and consider pharmacological prevention only for carefully selected high-risk individuals.^{1,15,19,20}

What is reversible?

The lecture positioned prediabetes as active pathophysiology rather than a mild biochemical abnormality. Glucose variability, visceral adiposity, hepatic fat accumulation, and β -cell stress were presented within a broader narrative of reversibility. This framework aligns with the twin-cycle model, in which ectopic fat accumulation in the liver and pancreas contributes to insulin resistance and impaired insulin secretion, but can improve when metabolic load is reduced.⁷ This reversible sequence is summarised schematically in Figure 2.

The symposium also situated reversibility within a wider environmental context. Large-scale burden estimates suggest that exposure to fine particulate matter of 2.5 micrometres or less in diameter (PM_{2.5}) accounts for one fifth of the global type 2 diabetes burden. More recent evidence syntheses support associations between long-term exposure to PM_{2.5}, particulate matter of 10 micrometres or less in diameter (PM₁₀), nitrogen dioxide and ozone and incident type 2 diabetes.^{8,9} These findings reinforce that diabetes prevention cannot be reduced to individual willpower; clinical prevention must be complemented by policy action on environments that shape metabolic risk.

Prediabetes remission as a clinical target

A key scientific message was that prediabetes remission should be considered an explicit prevention endpoint. Prevention-trial evidence supports this position. In the original Diabetes Prevention Program (DPP), intensive lifestyle intervention reduced incident type 2 diabetes by 58%, while metformin reduced it by 31% compared with placebo.² Long-term follow-up in the Diabetes Prevention Program Outcomes Study (DPPOS) confirmed durable prevention effects over 15 years.³ DPP/DPPOS analyses further showed that regression from prediabetes to normal glucose regulation was associated with substantially lower future diabetes risk, including an approximately 56% reduction over 10 years in one analysis.⁴ Additional work linked regression to normoglycaemia with lower estimated cardiovascular risk and lower microvascular disease burden than persistent dysglycaemia.^{10,11}

Recent literature extends this concept. A 2025 study in *Nature Medicine* reported that prediabetes remission, even without overall weight loss, was associated with markedly lower subsequent type 2 diabetes risk, highlighting the importance of improved insulin sensitivity and favourable fat redistribution rather

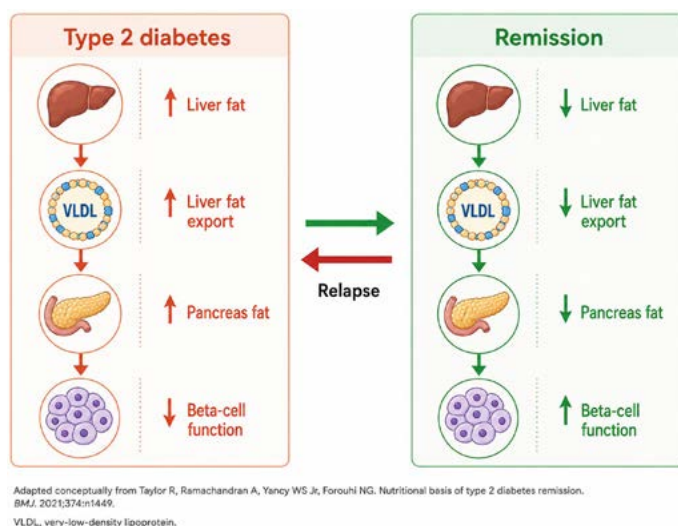


Figure 2: Author-created schematic of the twin-cycle model showing ectopic-fat and VLDL-mediated pathways in type 2 diabetes risk and remission. VLDL, very low-density lipoprotein.⁷

than body weight alone.¹² This evolving evidence base has been accompanied by an editorial call to define prediabetes remission as a distinct prevention endpoint, and by post-hoc analyses suggesting that remission may translate into lower cardiovascular morbidity and mortality over time.^{13,14} The symposium's emphasis on remission was therefore forward-looking, but grounded in an emerging evidence base.

Metformin: evidence-based adjunct, not a substitute for prevention care

The symposium also addressed metformin. Its central message was selective and evidence-aligned: metformin may have a role as an adjunctive option in selected adults with prediabetes who are at particularly elevated risk of progression. Current American Diabetes Association (ADA) standards state that metformin should be considered for prevention of type 2 diabetes in adults at high risk, as typified by the DPP, while the 2025 IDF recommendations include prevention and risk-reduction strategies within an adaptable framework for diverse care settings.^{1,15} This position is consistent with DPP evidence and pragmatic international practice, especially for younger adults with severe obesity, higher fasting glucose or glycated haemoglobin (HbA1c) values, and women with a history of gestational diabetes.¹⁻³

Lifestyle intervention remains foundational, metformin is adjunctive in selected high-risk individuals, and the two approaches should not be framed as interchangeable.^{1-3,15} Metformin should be discussed as part of shared decision-making that includes renal function, gastrointestinal tolerability, the possibility of vitamin B12 deficiency with long-term use, pregnancy intentions where relevant, patient preference and the availability of ongoing lifestyle support.^{1,19,20}

Fasting-based dietary strategies and insulin sensitivity

The symposium highlighted fasting-based dietary strategies as a potential means of improving insulin sensitivity, reducing hepatic fat, and supporting movement towards remission. This is biologically plausible, given the roles of energy balance, visceral adiposity, hepatic fat accumulation and β -cell workload in the dysglycaemic continuum.⁷ Current evidence suggests that intermittent fasting may offer cardiometabolic benefits broadly comparable to continuous energy restriction, while some data in steatotic liver disease suggest possible improvements in hepatic steatosis and insulin sensitivity.^{16,17}

Clinicians may consider fasting as one part of broader nutritional care, provided the approach is individualised, appropriately supervised, and tailored to the patient's clinical context. The approach should remain patient-centred and guided by safety, feasibility, cultural acceptability, food security, work patterns, co-morbidities, medicines, and available support. For most people with prediabetes, fasting may be best positioned as complementary to – not a replacement for – structured lifestyle intervention, physical activity, and sustained weight-management support. Fasting-based approaches should be avoided or used only with specialist guidance in individuals who are pregnant, frail, at risk of disordered eating, or using medicines that increase hypoglycaemia risk.^{1–3,13}

How to act in practice

In practice, the lecture suggests turning “prediabetes” into a practical, hopeful plan with clear follow-up. The message should neither alarm nor falsely reassure. A useful patient-facing phrasing is: “Your glucose is high enough for us to take seriously, but early enough for us to improve. Our goal is to help you return to normal glucose levels if possible.” This reflects the symposium's

central theme while keeping the conversation respectful, non-stigmatising and action oriented.

Local clinical vignette

The following vignette is fictional and holds no patient-identifiable information.

A 49-year-old woman from Tshwane attends a primary-care clinic for routine blood pressure follow-up. Her body mass index is 33 kg/m². She has a family history of type 2 diabetes and had gestational diabetes 14 years ago. Screening shows an HbA1c of 6.2% and a fasting plasma glucose of 6.3 mmol/L, both confirmed on repeat testing. The clinician frames the consultation around reversibility rather than blame, explaining that the results are an early metabolic warning sign rather than inevitable progression to type 2 diabetes. Together, they agree on a practical three-month prevention plan that includes modest weight loss where possible, 150 minutes of brisk walking per week in manageable sessions, reducing sugar-sweetened beverages, culturally selected meal planning, and addressing sleep and stress-related factors. They plan repeat HbA1c and fasting plasma glucose testing to assess progress. Because she has high-risk features, including obesity, a family history of type 2 diabetes, and a history of gestational diabetes, metformin is discussed as an adjunct to lifestyle intervention after renal function assessment and shared decision-making. The clinical goal is framed not only as delaying future diabetes but also as actively trying to restore normal glucose regulation where possible.^{1–4,15}

The practical approach in Table I is offered as the author's synthesis for South African practice and should not be read as a protocol specifically proposed by the symposium speaker.

Strengths of the symposium

The symposium had three notable strengths. First, it communicated urgency without fatalism, avoiding the passivity often associated with terms such as “borderline diabetes.” Secondly, it used

Table I. Author's pragmatic “how-to” synthesis for South African practice

Step	Practical action	Clinical note
1. Confirm and contextualise	Confirm dysglycaemia using locally accepted testing pathways; review symptoms, medicines, pregnancy status where relevant, family history, adiposity, blood pressure, lipids, and cardiovascular risk.	Prediabetes is a risk marker and a prevention trigger; interpret it within cardiometabolic risk. ^{1,19,20}
2. Name the goal	Use hopeful, concrete language: “The goal is to move your glucose back into the normal range where possible.”	Normoglycaemia predicts lower diabetes risk and more favourable vascular outcomes. ^{4,10,11,13,14}
3. Start structured lifestyle support	Offer a DPP-style plan: realistic weight reduction where needed, at least 150 minutes/week of moderate activity, resistance exercise where possible, nutritional counselling, sleep/stress review, and planned follow-up.	Structured, measurable, culturally acceptable and reviewable. ^{1–3,15}
4. Consider metformin selectively	Discuss metformin for high-risk adults, especially those with multiple risk features such as severe obesity, higher HbA1c or fasting plasma glucose (FPG) values, younger age, or a history of gestational diabetes; check renal function and tolerability.	Adjunct only in selected high-risk patients after safety review. ^{1–3,15}
5. Review and intensify	Reassess after approximately three months, repeat glycaemic measures according to clinical judgement, and refer or intensify if values progress, symptoms develop or risk is complex.	Avoid “diagnose and discharge”; review, escalate or refer.
6. Build the pathway	Use nurses, diabetes educators, group sessions, digital reminders, community resources, and clear referral criteria to make prevention repeatable rather than dependent on one enthusiastic clinician.	A repeatable pathway is needed; prevention cannot depend on one clinician. ^{18,19}

pathophysiology to support clinical communication: visceral fat, hepatic insulin resistance and β -cell stress were presented as practical explanatory tools rather than abstract concepts.⁷ Thirdly, it linked individual care to system-level priorities, including earlier detection, structured prevention pathways, primary-care support and policy commitment. This systems perspective is particularly relevant in low- and middle-income settings, where fragmented care pathways may undermine sound prevention advice.^{15,18,19}

A further strength was the ethical positioning of the lecture. The emphasis fell on lifestyle support, careful selection for metformin and avoidance of product-specific promotion. That approach is important in an industry-sponsored symposium: it allows the scientific and public health argument to stand on its own merits while supporting credibility with clinicians and readers.

Limitations and points requiring caution

Prediabetes remission is increasingly relevant, but it still requires standardisation regarding duration, biochemical criteria, and interpretation in relation to medication exposure.¹³ Prevention strategies should therefore be individualised rather than applied uniformly to all people with prediabetes. The 2025 IDF recommendations and ADA standards appropriately position structured lifestyle intervention as the foundation of prevention, with metformin considered as an added possibility for selected high-risk individuals.^{1,15}

Clinicians and health systems should interpret the symposium's forward-looking messages as clinically useful guidance for more proactive prevention, while ensuring that implementation is guided by the strength of the evidence, individual patient characteristics, safety considerations, feasibility, and local implementation capacity. Readers should therefore approach this article as a reflective opinion paper, rather than as a systematic review of all prediabetes interventions or as a substitute for local clinical guidelines.

Implications for South African clinical practice

For South African clinicians, the practical message is that prediabetes should trigger action, not observation alone. Clinicians can communicate risk in concrete but hopeful terms, support nutritional and physical-activity change, and review progress with the explicit aim of restoring normoglycaemia where possible. Structured lifestyle intervention is still the most effective first-line strategy, while metformin has a role in carefully selected high-risk individuals, especially where risk is high, lifestyle response is inadequate or prevention infrastructure is limited.^{1–3,15}

The broader challenge is implementation. Earlier case-finding, usable risk stratification tools, referral pathways, nurse- and diabetes-educator-led support, community-based programmes and digital or hybrid prevention models are needed if the reversible window is to become more than a compelling metaphor. This is consistent with South Africa's NCD policy direction, which emphasises prevention, people-centred care and strengthened care cascades for diabetes and other chronic diseases.^{18,19}

Call to action

- For individual clinicians: do not leave prediabetes as a passive label; confirm the result, explain reversibility, set normoglycaemia as the aspiration where possible, and schedule follow-up.^{1,4,13}
- For practices, academic societies, and SEMDSA-level implementation: develop simple prediabetes pathways that specify risk stratification, referral criteria, lifestyle support, metformin use, and repeat testing intervals.^{1,15,19,20}
- For health systems: invest in prevention infrastructure that can be delivered by multidisciplinary teams, including nurses, diabetes educators, dietitians, pharmacists, community health workers, and digital support tools.^{18,19}
- For policy and environmental action: treat diabetes prevention as more than individual counselling by addressing food environments, safe spaces for activity and air-pollution exposure as determinants of metabolic risk.^{8,9,18}

Conclusion

Overall, "Prediabetes: The Reversible Window" was a clinically relevant symposium that reframed prediabetes as an active prevention opportunity. Its strongest contribution was the insistence that normoglycaemia matters and that reversibility should be pursued deliberately, safely, and equitably. For South African practice, the symposium offered a constructive provocation: if prediabetes can be reversible in selected individuals, clinical systems should be designed to support early, structured, and equitable prevention. The next step is therefore clear: move from awareness to structured prevention, from risk labelling to regression- or remission-oriented prevention care, and from individual advice to pathways that make healthier metabolic trajectories achievable for patients in real-world South African settings.

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Conflicts of interest

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Data availability

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“When we heal the Earth, we heal ourselves.” — David Orr

Dr Seshnee Moodley

President, SAAHIP

Sustainability, most of us have probably come across this term both professionally and personally, but more recently it seems as though it is a buzzword, linked to environmental health and eco-friendliness. It is everywhere, on food packaging, clothing, television and reading material, to create awareness around its importance. Humans, the planet we live on, and economic stability all need to be balanced, and if it isn't, it can lead to resources being depleted, inequality, an unhealthy population and an overall collapse of the eco-system. Therefore, sustainability is not merely a buzzword, but rather a very important term that links together or guides practises that balance our environmental, economic and social needs. These practises include improving our waste, protecting our resources, recycling appropriately and implementing good economic practises, where we can meet the needs of the present without compromising future generations' wellbeing.



In 2015, The United Nations adopted the agenda for sustainable development, comprising of the 17 sustainable development goals (SDGs) ranging from economic to environmental issues. These SDGs are monitored and are responsible to encourage the community to work together to achieve success by 2030. A healthy planet ultimately depends on healthy people and therefore health is a central focus of SDG 3 which aims to ensure healthy lives of the population and promotion of well-being for all ages. A healthy population has equal access to healthcare, with overall well-being and good health outcomes, increased life expectancy and takes more into account than just the disease burden. The World Health Organisation (WHO) has committed to achieve this healthy population by addressing the SDGs. Increased environmental awareness helps to improve the overall well-being of the population and decreases the burden on healthcare, by ensuring people are healthy.

The healthcare sector contributes to environmental impacts and therefore sustainable healthcare needs to focus on reducing these

harms whilst enhancing patient outcomes. The ideal situation would be to move towards a world where one would receive good healthcare, with minimal impact on the environment. Choosing the right healthcare practices as a healthcare practitioner (HCP) or pharmacist can positively influence sustainability. However, there needs to be commitment from the entire healthcare team, with the health facility adopting environmentally friendly policies to allow for rational and efficient use of resources.

The pharmacist's role in healthcare is vast and integral. We are strategically positioned as an important member of the multidisciplinary team, being the medicine expert and trusted resource, equipped to deliver medicine information and health education to both patient and HCP. We therefore are valued contributors to sustainability in healthcare. Pharmacists already perform screening tests, manage patients and make necessary referrals; we can therefore educate and work together with other HCPs in driving these sustainability concerns. At SAAHIP we have continuously looked to our 4 foundational pillars for guidance i.e. **collaboration, shared vision, commitment, and innovation**, and it is these principles that will assist us in ensuring positive contribution and support to sustainable healthcare.

In the 2023 report from the International Pharmaceutical Federation (FIP), on the Sustainability in Healthcare: The Role of the pharmacist and pharmacy practice, it was highlighted that sustainability in healthcare is vital and that the pharmacist is a key role-player. Even though our role is significantly important, for it to be meaningful and impactful, pharmacists need to continuously develop themselves professionally, to stay ahead of the rapidly evolving healthcare landscape. The pharmacist also needs to step out of the confines and comfort of the dispensary and embrace technology.

So, what can a pharmacist do? The recommendation would be to firstly understand the concept of sustainability, what it means to you personally and the effect it may have on your present and future life. Then it is important to understand how healthcare and the pharmaceutical industry affect sustainability and the positive impact that you as a pharmacist can make. One needs to take the overall lifecycle of the medicine into consideration from its synthesis, packaging, distribution and disposal. The production of medicine itself can contribute negatively to sustainability by increasing the carbon

footprint and impacting the global climate negatively. Improper disposal of pharmaceutical waste can cause environmental and public health damage.

It has been shown in various studies and reports that improper disposal of medicines have been constantly polluting our environment, contaminating the aquatic system and soil. Pharmaceuticals can enter the environment via excretion and disposal, industrial discharge and through agricultural use. It is therefore imperative that there is pharmacovigilance that takes our eco-system into account. Therefore, the pharmacist is key to the concept of eco-pharmacovigilance – preserving the health of the planet through green pharmaceutical practises.

Some valuable suggestions to practise eco-pharmacovigilance:

1. Attend webinars and trainings on sustainable practises in healthcare and pharmaceutical practises
2. Implement energy saving practises in your pharmacy
3. Look for strategies that can improve the overall waste production in the pharmacy

4. Implement or ensure an efficient medicine disposal system
5. Look for ways to collaborate with other healthcare professionals
6. Encourage healthcare education on the topic, via outreach programmes in the pharmacy

The future of sustainable healthcare depends on us working together as a team, setting goals and working towards them. We need to decrease our environmental footprint, improve patient health and do all this whilst maintaining economic stability. We need to advocate for greener practises and ensure patient and HCP health education is offered. It is important that these sustainability processes and practises be included in the undergraduate curriculum and teaching programmes. The decreased impact on the overall environment helps with the global climate impact and this ultimately decreases the stressors on our health facilities as well. We are already pharmacovigilance experts; it is now time to embrace the upgrade to eco-pharmacovigilance experts. To stay alive and be healthy, we need a healthy environment, we all share this one Earth and we therefore all have the collective responsibility to ensure its sustainability.

SAAHIP at SAPHEX 2026

Aisha Adam

At the 2026 South African Pharmaceutical Exhibition (SAPHEX), held at the Sandton Convention Centre on 25 and 26 March, SAAHIP entered the conversation with a clear message: hospital pharmacy is not a passive service operating in the background of healthcare. It is a clinical, operational, digital and leadership force that shapes the quality of patient care.

The broader theme of SAPHEX 2026, Uniting Healthcare Professionals, found expression in the SAAHIP session, Celebrating Success Stories in Hospital Pharmacy: Demonstrating Value, Innovation and Impact. It was a reminder that some of the most transformative change in healthcare begins when pharmacists look at broken systems and refuse to become acquainted with them.

Mr Kesentseng Mahlaba facilitated the SAAHIP session and played an important role in tying the programme together. His facilitation gave the session coherence, allowing the different presentations to speak to one another rather than stand as isolated success stories. In doing so, he helped frame the panel as a collective statement on the value of hospital and institutional pharmacists in strengthening healthcare systems.

From dispensing to decision-making: The evolving role of hospital pharmacists in clinical care

Although SAAHIP National President, Dr Seshnee Moodley, was unable to attend the session, her scheduled topic remained an important

framing point for the day. It captured the shift that the rest of the session went on to demonstrate through lived examples. Hospital pharmacists are no longer only custodians of medicines. They are decision-makers, system builders, clinical partners, innovators and advocates for safer care. The presentations that followed demonstrated this evolution in real time.

Collaborative pharmacy practice: Driving better patient outcomes through interdisciplinary models

Ms Kim Nagoor opened a crucial conversation on collaborative pharmacy practice in hospital care. Her presentation placed the modern hospital patient at the centre of the discussion. Today's hospitalised patients often present with multiple co-morbidities, complex medication regimens and heightened vulnerability to medication-related harm. In such an environment, no profession can safely work in isolation.

Ms Nagoor positioned the clinical pharmacist as a professional who sees the patient through the lens of medicine use, but never in isolation from the broader clinical picture. Through comprehensive medication reviews, pharmacists identify therapeutic duplications, interactions, contraindications, inappropriate doses and opportunities to optimise therapy. These interventions are clinical acts that reduce risk and support better health outcomes. Her presentation also highlighted the power of digital platforms in strengthening this work. Electronic

medical records, electronic prescribing, laboratory integration and secure communication channels allow pharmacists to access patient information in real time, identify medication-related problems earlier and engage with treating clinicians more efficiently. In this model, technology does not replace professional judgement. It expands the reach of clinical pharmacy and makes collaboration more immediate, visible and consistent.

One of the strongest messages from this presentation was that collaboration depends on trust. Trust is built through reliable recommendations, evidence-based communication, proper documentation and follow-up. It is built when pharmacists consistently show up with clinical value, and when health systems create the space for that value to be recognised.

Stewardship culture: Successes from antimicrobial stewardship teams in public sector hospitals

Ms Lebogang Molepo's presentation on antimicrobial stewardship (AMS) in public sector hospitals shifted the conversation from collaboration in theory to collaboration under pressure. Her presentation addressed antimicrobial resistance as one of the defining health threats of our time.

The strength of the presentation was that it did not frame AMS as a technical exercise alone. It framed stewardship as culture. Policies matter. Guidelines matter. Audits matter. But without a shared mindset of accountability, collaboration and sustainability, stewardship cannot become embedded in practice. Her presentation described an AMS model grounded in multidisciplinary participation, including doctors, pharmacists, microbiologists and infection control staff. It also showed how governance structures can make stewardship sustainable. The presentation reminded attendees that measurement matters. Audits, antibiograms, antimicrobial use reports and resistance pattern monitoring allow teams to move beyond assumptions and work with evidence. Data becomes a mirror. It reveals where systems are improving, where they are still failing and where attention must go next.

Ms Molepo was courageous in addressing the barriers. Time, staffing constraints, knowledge gaps, institutional resistance, lack of diagnostics, resource limitations and resistance to change were all named. Her recommendations were practical and future-focused: use

digital tools for surveillance and training, extend stewardship awareness to outpatient settings, improve staffing and stock availability, embed AMS into routine ward rounds and pharmacy reviews, and strengthen the role of clinical pharmacists in public hospitals. The fundamental message was that stewardship is not only about protecting antibiotics. It is about protecting the future of care.

Leading change from within: Pharmacists as innovators in resource-constrained hospital settings

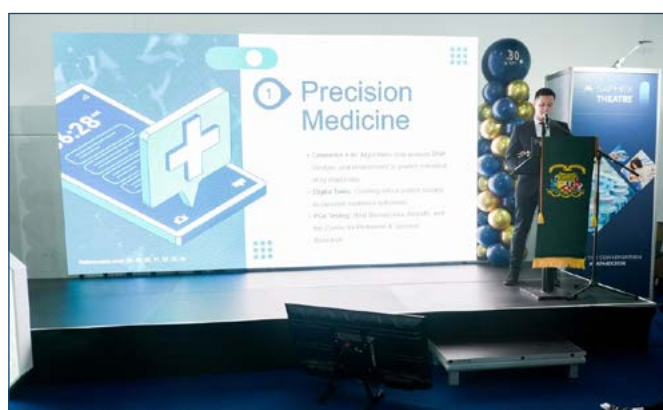
If Ms Nagoor's presentation showed the clinical value of collaboration, and Ms Molepo's presentation showed the discipline of stewardship, Mr Bandela Mgoqi's presentation showed the emotional cost of broken systems and the resilience it takes to redesign them. His presentation centred on the development of SkipTheQ, a digital solution aimed at reducing waiting times for chronic medication collection at Kalafong Tertiary Hospital.

The presentation began with a story. A patient, frustrated in an overcrowded outpatient pharmacy, became agitated while waiting for medication. The situation forced a difficult but necessary realisation: the problem was not only the patient, nor the staff, nor a lack of care. The problem was the system. SkipTheQ was presented as a response to that reality. The design allows patients to book chronic medication collection through a web-based platform or WhatsApp. Medication is prepared in advance, and patients are able to collect within 15 minutes. The target population includes patients who cannot afford to wait, patients who are not eligible for CCMDD and patients who cannot be down-referred. The reported results were significant. Waiting times decreased from 120 minutes to 50 minutes, placing the service below the provincial target of 60 minutes. More than 7 400 patients were served through the project.

The most memorable part of the presentation was the philosophy behind SkipTheQ, which was described as a redesign of access to medication. It removes unnecessary waiting and restores dignity to the patient. SkipTheQ is a testament to what can happen when pharmacists reject the self-perception of just being workers inside systems and begin acting as designers of better ones.

A shared message across the session

Across all three presentations, a shared landscape of hospital and institutional pharmacy emerged. In Ms Nagoor's presentation,



the pharmacist was a clinical partner who improves care through medication expertise, digital tools and multidisciplinary relationships. In Ms Molepo's presentation, the pharmacist was a steward of antimicrobial effectiveness, using governance, culture, data and persistence to protect future treatment options. In Mr Mgoqi's presentation, the pharmacist was an innovator who transformed frustration into a practical access solution.

Different contexts. Different problems. Same underlying principle. Pharmacists are builders.

Builders of safer prescribing systems. Builders of stewardship culture. Builders of digital solutions. Builders of trust between professions. Builders of healthcare systems that are more responsive, more humane and more capable of serving the communities that depend on them.

At SAPHEX 2026, SAAHIP did more than celebrate success stories. SAAHIP reinforced a message: the future of the profession will not be built by accepting broken systems as preordained fate. It is built by professionals willing to enter those systems, understand them, challenge them and transform them from within.

SAAHIP's wider footprint at SAPHEX 2026

SAAHIP's presence at SAPHEX 2026 also extended beyond its dedicated session, reflecting the breadth of leadership, expertise and influence held by its members across the wider pharmacy profession. Several SAAHIP members contributed to other sessions throughout the exhibition, carrying the association's voice into conversations on digital health, mentorship, public sector reform and young pharmacist leadership.

Mr Brent Sin Hidge presented on Practical Digital Tools for pharmacists in South Africa during the SAACP session on The Future Pharmacist's Toolkit. Mr Nhlanhla Mafarafara contributed to the panel discussion on National Health Insurance through his presentation on Public Sector: System Alignment. Within the Young Pharmacists' Group (YPG) session, Ms Telicia Jobraj presented on the journey From Mentee to Mentor, Mr Stanley Morapedi presented on Digital Health Promotion, Ms Aisha Adam presented on Bridging Generations within the profession, and Mr Kevin Baloyi served as a YPG session facilitator. Together, these contributions showcased how SAAHIP members actively led conversations across different areas of practice.

MenQuadfi now available in South Africa to help protect against invasive meningococcal disease caused by serogroups A, C, W and Y



The quadrivalent meningococcal conjugate vaccine provides healthcare professionals with an additional vaccination option for individuals from 12 months of age.

Johannesburg, 17 August 2026: Sanofi is pleased to announce the launch of a new innovation in vaccination against invasive meningococcal disease (IMD).¹

MenQuadfi is now available in South Africa for active immunisation against IMD caused by *Neisseria meningitidis* serogroups A, C, W and Y in individuals aged 12 months and older.¹

MenQuadfi provides healthcare professionals with an enhanced MenACWY vaccine¹ against a disease that can progress rapidly³ and whose epidemiology continues to evolve around the world.²

MenQuadfi replaces Menactra as an innovative solution in the fight against IMD,¹ and:

- MenQuadfi is registered in over 80 countries worldwide with ~23 million doses distributed globally.¹²
- Offers a tetanus toxoid protein carrier, an alternative to the diphtheria toxoid carrier that is in Menactra. This carrier allows for higher polysaccharide-to-protein (PS:PR) ratios, which enhances immune responses – which is especially evident in serogroup C antibody responses in toddlers.¹³
- Provides a ready-to-use formulation – a practical advantage to aid in eradication of potential administration errors.¹⁴
- Offers 10 µg of antigen per serogroup vs. 4 µg for Menactra. The 2.5-fold higher concentration in MenQuadfi provides robust protection against IMD, particularly for serogroup C in adolescent populations.¹⁵
- Offers a simplified dosing schedule: single dose from 12 months of age onward.¹

IMD is a potentially life-threatening infection that can present primarily as meningitis or septicaemia. Global research shows that its incidence and the serogroups responsible vary considerably between countries and over time. Six serogroups – A, B, C, W, X and Y – are responsible for nearly all incidences of IMD worldwide, while shifts in circulating serogroups have changed vaccination strategies in a number of countries.²

The speed at which the disease can progress adds to the clinical challenge. A prospective study of 448 children and adolescents with meningococcal disease found that most initially presented with non-specific symptoms during the first four to six hours of illness, yet could be critically ill by 24 hours.³

South African surveillance from 2003 to 2016 recorded an in-hospital case-fatality rate of 17%, while published South African recommendations report that approximately 20% of survivors may experience long-term sequelae including hearing loss, amputations and neurological complications.^{10,11}

Age also influences meningococcal epidemiology. While disease incidence is high in young children in many settings, adolescents and young adults play an important role in transmission. A systematic review and meta-analysis found that meningococcal carriage increased from 4.5% in infants to a peak of 23.7% at age 19 before declining again through adulthood.⁴

"IMD can be difficult to recognise early because the first symptoms may look like those of other common infections," says Diane Buron, Medical Head for Vaccines at Sanofi South Africa. "Its rapid progression means prevention remains a critical part of reducing the burden of disease. The changing distribution of meningococcal serogroups also makes it important to understand which serogroups a vaccine covers when making vaccination decisions."

South African epidemiology adds to the global picture

South African research reflects the wider finding that meningococcal epidemiology is dynamic and that several serogroups contribute to disease.

A study using national laboratory-based surveillance identified 585 cases of IMD in South Africa between 2016 and 2021. A capsular group could be determined in 477 cases. Serogroup B accounted for 44% of these cases, while W, Y and C combined amounted to 54% (24% for W, 20% for Y and 10% for C).⁵

These findings provide local context for clinicians, while also underlining an important distinction between available meningococcal vaccines and the serogroups they cover.

MenQuadfi is a quadrivalent meningococcal tetanus toxoid-conjugate vaccine that targets serogroups A, C, W and Y. It does not protect against other *N. meningitidis* serogroups, including serogroup B.¹

Clinical evidence across age groups

The clinical evidence for MenQuadfi, referred to as MenACYW-TT in published studies, includes trials in toddlers, adolescents, adults and older adults.

In a phase III randomised study of 918 toddlers aged 12 to 23 months, a single dose of MenACYW-TT was compared with another licensed quadrivalent meningococcal tetanus toxoid-conjugate vaccine. MenACYW-TT demonstrated non-inferior seroprotection against serogroups A, C, W and Y 30 days after vaccination in meningococcal vaccine-naïve toddlers and in the overall population, which included children previously vaccinated against meningococcal serogroup C. Safety profiles were comparable between the vaccine groups.⁶

A phase IIb study in 463 healthy adolescents aged 10 to 17 years also demonstrated non-inferior seroprotection against all four serogroups compared with another quadrivalent MenACWY vaccine. Immune responses were comparable when MenACYW-TT was administered alone or concomitantly with Tdap-IPV and 9-valent HPV vaccines.⁷

Evidence in older adults comes from a phase III randomised study in people aged 56 years and older. MenACYW-TT demonstrated non-inferior seroresponses against A, C, W and Y compared with a quadrivalent meningococcal polysaccharide vaccine and was well tolerated.⁸

Longer-term follow-up has also examined persistence of the immune response. A 2025 study followed children who had received MenACYW-TT five years earlier as toddlers. Antibody levels and seroprotection rates remained higher than those recorded before primary vaccination. After a booster dose, seroresponse rates ranged from 93.2% to 98.9% across serogroups A, C, W and Y, with no new safety concerns identified.⁹

"The availability of MenQuadfi in South Africa enhances the options healthcare professionals have when considering MenACWY vaccination for appropriate patients," says Buron. "The clinical programme has demonstrated high immune responses across different age groups, while the quadrivalent formulation provides coverage against four clinically important meningococcal serogroups."

Supporting informed vaccination decisions

For healthcare professionals, meningococcal vaccination requires consideration of the individual patient alongside circulating disease patterns and the serogroups covered by a particular vaccine.

Published South African recommendations identify people with complement deficiencies or anatomical or functional asplenia, laboratory personnel routinely exposed to *N. meningitidis* and travellers to hyperendemic or epidemic regions as groups for whom meningococcal vaccination is recommended. They also advise clinicians to consider vaccination for adolescents and young adults entering university, college or military training, particularly those living in communal accommodation, as well as other people whose medical or living circumstances may increase their risk.¹¹

MenQuadfi is indicated for active immunisation of individuals from 12 months of age against IMD caused by *N. meningitidis* serogroups A, C, W and Y. The use of the vaccine should be in accordance with available official recommendations.¹ For further information, health care professionals can refer to the approved Professional Information.

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Sun Pharma launches generic semaglutide in South Africa



Johannesburg, 21 July 2026 — Sun Pharmaceutical Industries Limited (Reuters: SUN.BO, Bloomberg: SUNP IN, NSE: SUNPHARMA, BSE: 524715) (together with its subsidiaries and/or associated companies, "Sun Pharma") today announced the launch of generic semaglutide, a once-weekly GLP1 receptor agonist, in South Africa for the treatment of adults with inadequately controlled type 2 diabetes mellitus as an adjunct to diet and exercise.

The product is supplied in a prefilled, multidose injectable pen in two strengths (2 mg/1.5 mL and 4 mg/3 mL) that allow flexible, once-weekly dosing. The device features a smooth dialer for accurate dose selection and a concealed needle to improve handling safety and reduce injection anxiety. The pens are manufactured in Europe and developed with established pharmaceutical device suppliers.

"Type 2 diabetes remains a major public health challenge in South Africa," said Malcolm Brown, Chief Executive Officer, Sun Pharma South Africa. "The availability of generic semaglutide strengthens the range of evidence-based treatment options available to clinicians and patients. Our objective is to support better clinical outcomes by improving access to proven therapies that can be integrated into comprehensive diabetes care."

Clinical context and public health relevance

- Type 2 Diabetes remains one of South Africa's most significant public health challenges. As per the International Diabetes Federation country report, it is estimated that 3.9 million patients aged 20-79 would be living with diabetes in South Africa by 2050.
- South Africa faces a growing burden of type 2 diabetes, driven in part by rapid urbanization and changing lifestyles. This rising

prevalence places significant pressure on patients and healthcare services. Improving access to effective therapies is therefore an important component of addressing this national health challenge.

- With the launch of generic semaglutide in South Africa, Sun Pharma aims to provide clinicians and patients with an additional licensed option for comprehensive diabetes management, supporting better long-term outcomes when used alongside diet and exercise.

Regulatory and medical review

Healthcare professionals are advised to consult full prescribing information and local treatment guidelines when considering semaglutide for individual patients. The company's local medical team is available to assist clinicians with scientific inquiries and product information.

About Sun Pharmaceutical Industries Limited. (CIN - L24230GJ1993PLC019050)

Sun Pharma is a leading global pharmaceutical company with a presence in Innovative Medicines, Generics and Consumer Healthcare products. It is the largest pharmaceutical company in India and is a leading generic company in the US as well as Global Emerging Markets. Sun's high growth Global Innovative Medicines portfolio spans innovative products in dermatology, ophthalmology, and onco-dermatology and accounts for about 22% of company sales. The company's vertically integrated operations deliver high-quality medicines, trusted by physicians and consumers in over 100 countries. Its manufacturing facilities are spread across five continents. Sun Pharma is proud of its multi-cultural workforce drawn from over 50 nations. "For further information, please visit www.sunpharma.com and follow us on LinkedIn & X (Formerly Twitter)."

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Diabetes management

1. Which of the following best describes the underlying cause of type 1 diabetes mellitus?

- a Progressive insulin resistance caused by obesity
- b Chronic inflammation causing impaired glucose absorption
- c Reduced incretin hormone secretion during pregnancy
- d Autoimmune destruction of pancreatic β -cells resulting in absolute insulin deficiency

2. Which of the following is recommended as first-line pharmacological therapy for the management of type 2 diabetes mellitus?

- a Semaglutide
- b Metformin
- c Empagliflozin
- d Pioglitazone

3. Which aspect of diabetes management requires pharmacists to provide hands-on patient training?

- a Interpretation of HbA1c results
- b Correct use of insulin pens and injection technique
- c Dietary carbohydrate planning
- d Blood pressure monitoring

4. Which of the following lifestyle interventions has been shown to provide the greatest improvement in metabolic outcomes for patients with type 2 diabetes mellitus?

- a Aerobic exercise only
- b Resistance exercise only
- c Combined aerobic and resistance exercise
- d Combined aerobic exercise and flexibility training

Anti-obesity medications for the management of obstructive sleep

5. Which non-pharmacological treatment remains the current gold standard for the management of obstructive sleep apnoea (OSA)?

- a Bariatric surgery
- b Continuous positive airway pressure (CPAP)
- c Tirzepatide
- d Liraglutide

6. What is the primary mechanism by which anti-obesity medications improve obstructive sleep apnoea in most patients?

- a Direct stimulation of upper airway muscles
- b Reduction of airway inflammation only
- c Weight loss leading to reduced upper airway
- d Increased oxygen delivery during sleep

7. Which anti-obesity medication became the first pharmacological agent approved by the US Food and Drug Administration (FDA) specifically to treat moderate-to-severe obstructive sleep apnoea (OSA) in adults with obesity?

- a Semaglutide
- b Liraglutide
- c Phentermine/topiramate
- d Tirzepatide

8. According to the current evidence, why should anti-obesity medications not be considered a universal standalone treatment for obstructive sleep apnoea?

- a They are ineffective at producing weight loss
- b Obstructive sleep apnoea has multiple underlying mechanisms, and not all patients have obesity as the primary cause
- c They are approved only for use in patients with type 2 diabetes
- d They are recommended only after bariatric surgery

Optimising prevention of shingles with vaccination: Considerations for pharmacists

9. Which clinical feature is most characteristic of shingles?

- a Bilateral itchy rash involving the entire body
- b Painful unilateral vesicular rash confined to a dermatome
- c Diffuse maculopapular rash with fever
- d Generalised pustular eruption

10. A 50-year-old patient reports having had shingles five years ago. What is the most appropriate recommendation regarding shingles vaccination?

- a Vaccination is unnecessary because shingles occurs only once
- b Vaccination should be avoided permanently after shingles
- c Vaccination is still recommended because shingles can recur
- d Vaccination should only be given after another episode

11. Which of the following is the primary goal of shingles vaccination?

- a Eliminate latent varicella-zoster virus from sensory ganglia
- b Prevent chickenpox in children
- c Reduce the risk of shingles and postherpetic neuralgia
- d Cure established postherpetic neuralgia

12. Which of the following individuals have the highest risk of developing shingles?

- a Healthy 20-year-old adult
- b Healthy child vaccinated against varicella
- c Adult aged 65 years with diabetes mellitus
- d Pregnant woman aged 30 years

A sore throat, not a sore point: Evidence-based management of acute tonsillitis

13. A 7-year-old child presents with acute tonsillitis and complains of a sore throat, painful swallowing, and fever. Which of the following over-the-counter oral analgesics is effective in reducing pain after a single dose and is safe to administer to children?

- a Tramadol
- b Diclofenac
- c Paracetamol
- d Erythromycin

14. Which of the following is the first-line antibiotic prescribed for symptomatic treatment of acute tonsillitis?

- a Cephalexin
- b Penicillin
- c Amoxicillin
- d Erythromycin

15. Which drug class may be prescribed as adjuvant therapy to reduce inflammation and throat pain in severe acute tonsillitis?

- a Antibiotics
- b Herbal medicine
- c Throat sprays
- d Corticosteroids

16. A 28-year-old pregnant woman presents with acute bacterial tonsillitis. She has a documented immediate hypersensitivity (anaphylactic) allergy to penicillin. Which of the following antibiotics is the most appropriate alternative?

- a Clindamycin
- b Cefadroxil
- c Cephalexin
- d Erythromycin

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 • Volume 3 • 2026

1. c 2. b 3. a 4. c 5. d 6. b 7. b 8. c 9. d 10. b 11. c 12. a 13. b 14. d 15. b
16. c 17. c 18. c 19. d 20. b



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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

- **AndroGel**[®] provides rapid effects, with no ups and downs in effectiveness, reaching steady state on Day 2
- Testosterone levels are maintained within the physiological range with a daily application
- Testosterone concentrations return to baseline 72-96h after the final dose

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



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 Clin Endocrinol Metab 2000;85:2839-2853; 3. Wang C et al. J Clin Endocrinol Metab 2004;89:2085-2098; 4. Behre HM et al. Aging Male 2013;15:198-207

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