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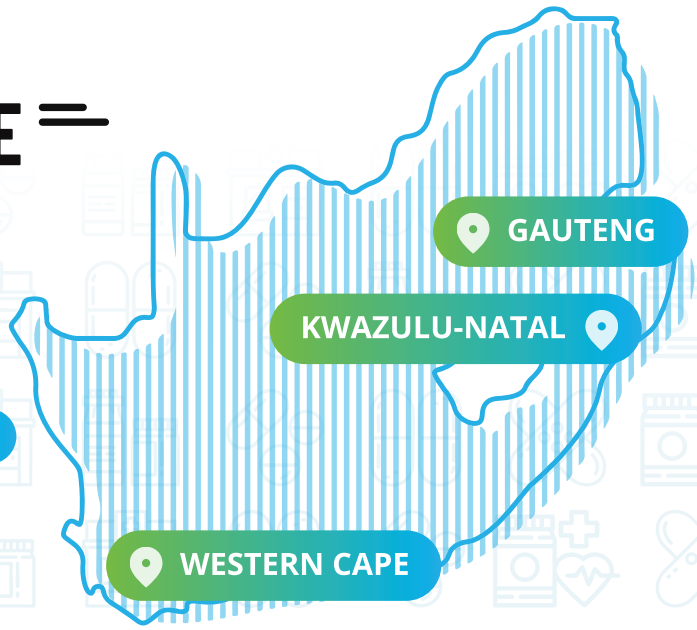

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Cheryl Stulting (Medpharm)
E-mail: cheryl@medpharm.co.za

SUBSCRIPTION
info@medpharm.co.za

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The Pharmaceutical Society of South Africa,
435 Flinders Avenue, Lynnwood, 0081
PO Box 75769, Lynwood Ridge, 0040
Tel: (012) 470 9550, Fax: (012) 470 9556
www.pssa.org.za
E-mail: nitsa@pssa.org.za

Medpharm Publications

Medpharm Publications,
Ground Floor, Centurion Wine & Art Centre,
123 Amkor Road, Lyttelton Manor
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SAPJ Author Guidelines

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

Aims, scope and review policy

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

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

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

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

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

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Access or excess? Peptide manufacturing pharmacies at the fault line of South African pharmacy professionalism

If you listen carefully to how members of the pharmacy profession within South Africa is speaking about itself now, a pattern emerges. In this edition you will learn that hospital colleagues are writing about evolution from basements/dispensaries to the bedside, about stewardship, innovation and learning from the giants who came before them. Young pharmacists are insisting that relevance and purpose matter more than where on the programme their session appears, and are asking older pharmacists and mentors, hard questions about mentorship, digital health and leadership. Educators are reflecting deeply on how we shape professional identity, not only competence, under conditions of uncertainty and constraint. I believe this will be a constant, the uncertainty and constraint as change is a constant; what matters ethically is not whether we can escape it, but whether we respond to it deliberately and responsibly, in ways that honour our obligations to patients, colleagues and the public.

Change in science and practice rarely arrives in a neutral form; it is carried concrete technologies, products and business models that test how serious we are about our own standards. Over the past two years, incretin-based peptides such as semaglutide and tirzepatide have moved from specialist diabetes clinics into the public imagination as weight-loss "super-drugs". They are now widely promoted as weight-loss injections on social media and offered in some private and aesthetic settings, including certain pharmacy spaces, despite repeated warnings about unregistered GLP-1 products sold via informal and online channels. Nowhere is this more visible than in the rapid rise of incretin-based therapies. What began as specialist tools for complex type 2 diabetes and high-risk metabolic disease has, in a few short years, become a powerful commercial force, reshaping **patient expectations** and placing new pressures on pharmacists, prescribers and regulators alike. It is in this tension between clinical promise, market enthusiasm and regulatory boundaries that the profession's ethical commitments are most clearly exposed.

A limited exception is created in section 14(4), read with regulation 3 of the General Regulations, which permits a pharmacist to compound a medicine for a specific, identified patient, on the basis of a valid prescription, in a quantity related to that individual's treatment and which does not amount to ongoing batch manufacture for the market. Section 14(4)(b) further requires that the active ingredient used in such compounding is already contained in at least one medicine registered in terms of the Act, and the regulatory literature is clear that compounding may not be used to circumvent the registration pathway. A limited exception is created in section 14(4), read with the General Regulations, which permits a pharmacist to compound a medicine for a specific, identified patient, on the basis of a valid prescription, in a quantity that is related to that individual's treatment and which does not amount to ongoing batch manufacture for the market. The same framework requires that the active ingredient used in such compounding is already contained in at least one registered medicine, and that compounding may not be used to circumvent the registration pathway.

Good Pharmacy Practice (GPP) and Good Manufacturing Practice (GMP) operate together, but they do not apply to the same activities. GPP is issued by the South African Pharmacy Council (SAPC) as *"Rules relating to Good Pharmacy Practice"* under section 35A of the Pharmacy Act 53 of 1974, and it sets the minimum standards for all pharmacy premises and services, including extemporaneous compounding. These rules require that any compounded medicine be prepared in suitable premises, using appropriate equipment, with documented standard operating procedures, quality-assurance systems, and full records, and they reiterate that extemporaneous preparations are exceptional, patient-specific and based on a valid prescription, not a mechanism for routine batch production. Extemporaneous compounding is further constrained by the Medicines and Related Substances Act 101 of 1965 and its General Regulations, which permit compounding only within the narrow exemption in section 14(4), for quantities related to an individual patient's treatment and using active ingredients that are already present in at least one registered medicine. By contrast, GMP, as defined in SAHPRA's South African Guide to Good Manufacturing Practice for Medicines, applies to licensed manufacturers of finished products, including sterile peptide injectables, and requires a level of validated process control, environmental monitoring and batch-release testing that goes well beyond what is envisaged for a pharmacy compounding unit.

SAHPRA is a participating authority in the Pharmaceutical Inspection Co-operation Scheme (PIC/S), which means South African manufacturers are expected to meet internationally aligned GMP standards.

Within this combined framework, a pharmacy that compounds occasionally for named patients is expected to comply with GPP and

with the compounding conditions in section 14(4) of the Medicines Act; it is not expected to operate to full GMP standards. However, once a pharmacy begins to prepare unregistered glucagon-like peptide-1 (GLP-1) receptor agonists or dual GIP/GLP-1 receptor agonist injections in bulk, for commercial distribution, it no longer fits within the legal definition of extemporaneous compounding. It is effectively functioning as a manufacturer without a manufacturing licence, without registered products under section 14(1), and without compliance with SAHPRA's GMP expectations. They are now widely promoted as weight-loss injections on social media and offered in some private and aesthetic settings, despite SAHPRA warnings about unregistered GLP-1 products sold through informal and online channels.

Within this combined framework, the routine preparation of unregistered glucagonlike peptide1 (GLP1) receptor agonists or dual GIP/GLP1 receptor agonist products in bulk, for commercial distribution, does not fall within lawful extemporaneous compounding; it is treated in law as the manufacture and sale of unregistered medicines in contravention of section 14(1) of the Medicines Act and outside both GPP and applicable GMP requirements.

SAHPRA's 2025 RC03 communication moves further in relation to incretin-based peptides. In that notice, the Authority announces its intention, in terms of section 23 of the Medicines Act, to declare medicines compounded under section 14(4) that contain GLP-1 active components, or combinations of GLP-1 and gastric inhibitory (glucose-dependent insulinotropic) polypeptide (GIP) agonist components, to be "undesirable", on the basis that their extemporaneous preparation is not in the public interest. In such circumstances, the legal position is not ambiguous, the entities involved are operating outside the compounding exemption, manufacturing unregistered medicines in contravention of the Medicines Act 101 of 1965 and breaching professional rules under the Pharmacy Act.

The SAPC Code of Conduct requires that the wellbeing of the patient and the public remain the pharmacist's prime concern, that professional independence be maintained, and that pharmacy professionals avoid perverse incentive arrangements that place self-interest or commercial gain above lawful, ethical, and safe practice.

In a strictly legal or commercial reading, patients appear primarily as *"demand drivers"* for weight-loss injections. In an ethical reading, they appear as people with complex histories of stigma, failed treatments, and often carry deep shame around obesity and metabolic disease. An empathetic posture recognises that such patients are particularly vulnerable to promises of "quick fixes" and may struggle to appraise risk in the face of hope. Ethical pharmacy practice, especially in a resource-constrained system, therefore, asks not only "can I provide this product?" but "what does it mean to offer this to this person, in this context, with this level of evidence uncertainty?". Empathy here is not sentimentality; it is a disciplined willingness to see the patient's vulnerability clearly, to recognise our own power in the interaction, and to act in ways that protect rather than exploit that vulnerability.

Bringing these strands together, a coherent ethical framework for South African pharmacy would include at least three commitments. First, *a deontological commitment* to the Code of Conduct and GPP, the patient's wellbeing and public health come before profit and convenience; we do not enter into perverse arrangements even when they are lucrative. Second, an *evidence-based commitment*, we do not manufacture, promote or dispense medicines whose quality, safety and efficacy have not been established through appropriate regulatory pathways, particularly when regulators have explicitly declared them undesirable. Third, an *empathy-infused, relational commitment* we refuse to turn patients' desperation and structural barriers to care into a market opportunity, and we consciously design our services, whether in obesity, diabetes or any other field to support dignity, informed choice and shared decision-making rather than dependency and risk. Not just lip service.

Seen through this ethical lens, the GLP-1/peptide story is not primarily about "bad apples" caught in a regulatory net. It is a stress test of our collective moral posture as a profession that prides itself on science, stewardship and patient-centred care. Our response will signal to our students, our colleagues and our regulators whether we are prepared to align our incentives with our ethics, and our practice with both the law and the people it is designed to protect.

At a system level, we need clearer, practical guidance on the regulatory status of peptide products, particularly biologics and dualagonist combinations. We need transparent, sciencebased criteria for when local manufacturing is in the public interest and what standards must be met. We need closer alignment between SAHPRA, SAPC, professional bodies and academic partners, so that policy, education and practice do not pull in different directions. At a practice level, pharmacy owners and responsible pharmacists must subject their own business models to honest scrutiny. Does this service align with GPP, our Code of Conduct and our commitments to safety and equity?

Crucially, we must not treat the current peptide debate as an isolated compliance problem. It is taking place in a profession that is simultaneously expanding its roles in primary health care within the mandate of the National Health Insurance (NHI). I believe the real question before us is not whether local peptide innovation is inherently good or bad. It is whether any such innovation is embedded in lawful, transparent resilient needsbased models that genuinely improve access without compromising safety or equity. In a country where so many still lack reliable access to essential medicines and dependable pharmaceutical care, we have to be precise about what we mean by "access". If it simply means that those with means can buy unregistered injectables from whoever is willing to sell them, then we have not advanced access at all; we have merely packaged excess in clinical language. We have to be resilient in a market that changes so quickly.

Taken together, the legal and regulatory framework leaves little room for ambiguity. Section 14(1) of the Medicines Act establishes registration as the norm for all medicines, with section 14(4) creating only a narrow, patient-specific compounding exception; section 14(4)(b) and the General Regulations make clear that this exception is

constrained in both quantity and active-ingredient choice. SAHPRA's RC03 notice and subsequent GLP-1 warnings have now explicitly closed this exception for GLP-1 and GLP-1/GIP agonist products by signalling an intention to declare them "undesirable" when compounded and by treating their bulk production and promotion as unlawful manufacturing and distribution of unregistered medicines. At the same time, the SAPC Code of Conduct and GPP rules oblige pharmacists and registered support personnel to put patient and public wellbeing first, maintain professional independence, comply with all applicable legislation and avoid perverse incentive arrangements that place personal or commercial gain above legal and ethical duties.

For South African pharmacy, the evidence therefore points in one direction: large-scale "compounding" and marketing of unregistered GLP-1 and GLP-1/GIP peptides for weight loss cannot be reconciled with the Medicines Act, SAHPRA's regulatory stance or the profession's own Code of Conduct. Whatever debates continue about access and innovation in diabetes and obesity care, they must occur within the framework of registered products, licensed manufacture and lawful, evidence-based practice if pharmacy is to retain its claim to stewardship, integrity and public trust.

Natalie Schellack
Editor: SA Pharmaceutical Journal

SILVERLAB

The First Line of Viral Defence: Why Localised Nasal Intervention is Essential

The nasal mucosa serves as the primary biological gateway for respiratory viruses. For the pharmacist, managing winter ailments effectively requires a strategy that neutralises these pathogens at the point of entry. Silverlab Healthcare's Nasal Spray, formulated with pharmaceutical-grade ionic Silver (Ag^+), offers a targeted approach to localised viral defence without the risks associated with traditional decongestants.

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Pharmacists can recommend Silverlab with confidence, backed by data demonstrating rapid activity against high-priority respiratory threats:

- SARS-CoV-2: Independent research conducted by the CSIR (2021) confirmed that the Silverlab formulation achieves a 4-log (99.99%) reduction in viral load within only 60 seconds.
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Safe, Prolonged Daily Use

Unlike many over-the-counter nasal sprays, Silverlab is specifically designed for long-term support. It contains no cortisone, steroids, or harsh chemicals, ensuring it is safe for prolonged daily use **without the risk of rebound congestion** or dependency forming. This makes it an ideal prophylactic tool for high-exposure winter months

Multi-modal Action: Beyond Antimicrobial

A common challenge in treating nasal congestion is the underlying inflammatory response. Silverlab's ionic silver provides additional therapeutic benefits:

- Inflammatory Modulation: Clinical assays demonstrated that ionic silver down-regulates pro-inflammatory cytokines IL-6 and TNF-α by a factor of five, assisting in mitigating tissue damage associated with viral inflammation.
- High Bio-availability: The formulation consists of 97.4% ionic silver, ensuring active Ag+ ions are immediately available for bio-activity upon application.

Uncompromising Safety for Sensitive Tissues

- Non-Cytotoxic: Assays on human A549 lung cells showed zero toxicity (tested at 18x normal use strength), confirming a high safety profile for delicate respiratory membranes
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Clinical Advantages for Pharmacists

Silverlab Nasal Spray represents a scientifically validated alternative to generic decongestants and unregulated silver products.

By delivering localised 4-log (99.99%) viral-reduction and modulating the inflammatory response, it enables pharmacists to provide a proactive, long-term, non-toxic solution for respiratory health during the winter season.

Nasal Defence Summary:

- 99.99% viral reduction (SARS-CoV-2) in 60s.
- Non-toxic to human lung and kidney cell lines.
- Inhibits inflammation by down-regulating IL-6/ TNF-α.
- High bio-availability with 97.4% ionic silver content.
- No rebound effect: Safe for daily use, free from steroids and cortisone.

No rebound effect: Safe for daily use, free from steroids and cortisone.

Most viral infections start in the nose

Silverlab Nasal Spray

Safe for prolonged use

- ✓ *Prevents & manages nasal infections naturally*
- ✓ *No rebound congestion or dependency*
- ✓ *Safe for children*
- ✓ *Fast relief from allergies & hay fever symptoms*

SILVERLAB

Silverlab 18 ppm ionic (Ag^+) Silver Nasal Spray is highly effective with powerful antimicrobial and anti-inflammatory properties. Designed to combat airway infections, it offers a safe and natural way to maintain clear and healthy nasal passages for both adults and children.

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President's Message

Celebrating 80 years of organised pharmacy in South Africa

I have always liked birthdays. Not for the cake - although that helps - but for what happens just before the candles are blown out. There is usually a pause. People gather a little closer. Someone starts telling a story: "Do you remember when…?" And for a moment, time stretches. You are not only celebrating a number, but a life.

This year, the Pharmaceutical Society of South Africa turns eighty. Eighty years of organised pharmacy in South Africa is not simply about longevity. It is about continuity and commitment. Since its formal establishment in 1946, the PSSA has provided a space where pharmacists could come together, speak with a collective voice, and contribute to healthcare beyond the walls of their individual practices. Even before 1946, there was already a clear understanding among pharmacists that the profession needed unity and direction. That instinct to collaborate in service of both the profession and the public remains just as relevant today.

What makes pharmacy in South Africa distinctive is its diversity. It is not one type of practice, but many. Community pharmacists are often the most accessible healthcare professionals. Those in the public sector work within systems that demand resilience and adaptability. Clinical pharmacists bring depth and precision to patient care. Colleagues in academia and industry drive knowledge, research, and innovation. These are not separate tracks; they are interconnected parts of the same profession, each strengthening the other.

Pharmacy also occupies a unique position in the health system. It sits at the interface between medicines and patients, between policy and practice. This position carries both responsibility and opportunity. When pharmacy is actively engaged, access improves, safety is strengthened, and patient outcomes are better supported.

Over the years, the PSSA has helped to keep this collective effort aligned. By bringing different sectors together, the Society has supported professional development, contributed to policy discussions, and ensured that pharmacy remains an active participant in shaping healthcare in South Africa. It has also connected local practice to global conversations, allowing South African pharmacists to both learn from and contribute to the wider profession.

The role of pharmacy continues to expand. Pharmacists are increasingly involved in primary healthcare, from initiating treatment to supporting long-term patient management. There is growing engagement in areas such as antimicrobial stewardship, medicine safety, and the development of local pharmaceutical capacity. These are not small shifts; they represent a profession that is evolving in response to the needs of the health system.

Looking ahead, the next decade will require deliberate action. The pharmacy workforce must be supported and developed so that it can meet both current and future demands. Sustainable funding models will be needed to balance access with quality care. Innovation, particularly in areas like pharmacovigilance and data use, should be embraced to strengthen medicine safety. And within the profession, there is still work to be done in building stronger connections across sectors.

Yet, beyond all of this, the story of pharmacy is ultimately a human one. It is written every day by individuals: the pharmacist opening the pharmacy doors early in the morning, the colleague managing long queues in a busy clinic, the clinician reviewing medicines at the bedside, the academic guiding the next generation, and the young graduate stepping into practice for the first time.

So, as we mark this 80-year milestone, perhaps we return to that familiar birthday moment. The pause. The reflection. The stories. It is a time to acknowledge what has been built, to appreciate those who have contributed, and to consider what comes next.

There is much to be proud of, and even more to work towards. If the past eighty years have shown anything, it is that pharmacy in South Africa is at its best when it moves forward together.

Happy birthday, PSSA.

Renier Coetzee
PSSA President

80 Years of the PSSA: the Past, the Present and the Future

In 2026, the Pharmaceutical Society of South Africa (PSSA) proudly commemorated its 80th anniversary, a remarkable milestone that reflects eight decades of leadership, advocacy, and commitment to advancing the pharmacy profession in South Africa. This historic occasion was celebrated during SAPHEX 2026 through a dedicated commemorative programme that brought together local and global leaders, stakeholders, and members of the profession to reflect on the Society's journey and envision its future.

The celebration commenced with a formal welcome by the Master of Ceremony, Kesentseng Jackson Mahlaba, who set the tone for a reflective and forward-looking programme. This was followed by a powerful multimedia presentation that captured the evolution of the PSSA over the past 80 years. The presentation highlighted key milestones, including the Society's role in shaping professional standards, advocating for pharmacists, and supporting the development of pharmacy education and practice across various sectors.

PSSA 80th Anniversary Commemorative Stage at SAPHEX 2026

A special video message from the President of the International Pharmaceutical Federation (FIP), Paul Sinclair, underscored the global significance of the PSSA's contributions. His message acknowledged the Society's longstanding commitment to professional excellence and its alignment with international efforts to strengthen the role of pharmacists in healthcare systems worldwide.

Delivering the keynote address, PSSA President Prof Renier Coetzee, reflected on the theme: *"Honouring the Past, Strengthening the Present, Shaping the Future of Pharmacy"*. His address paid tribute to the pioneers of the profession while emphasising the importance of unity, innovation, and resilience in navigating the evolving healthcare landscape. He highlighted the critical role of pharmacists in improving patient outcomes and reinforced the need for the profession to remain adaptable and forward-thinking.

The commemorative programme was further enriched by messages from key stakeholders who play an integral role in the healthcare ecosystem. The Minister of Health, Dr Aaron Motsoaledi, delivered a pre-recorded message acknowledging the contribution of pharmacists to public health and the ongoing transformation of the healthcare system. Contributions from

80th birthday cupcakes

PSSA President Prof Renier Coetzee

Tammy Gopal of the South African Health Products Regulatory Authority (SAHPRA), Mogologolo Phasha, President of the South African Pharmacy Council (SAPC), and Mehboob Ali Cassim, Chairman of the Independent Community Pharmacy Association (ICPA), reinforced the importance of collaboration between regulatory bodies, professional organisations, and practitioners in advancing healthcare delivery.

A unique and defining feature of the celebration was the inclusion of reflections from the various sectors of the PSSA, showcasing the diversity and depth of pharmacy practice in South Africa. Representatives from the Academy of Pharmaceutical Sciences of South Africa (APSSA), the South African Association of Community Pharmacists (SAACP), the South African Association of Hospital and Institutional Pharmacists (SAAHIP), the South African Association of Pharmacists in Industry (SAAPI), and the Young Pharmacists' Group (YPG) shared insights into their respective domains. These reflections highlighted not only the progress made within each sector but also the shared commitment to excellence, patient care, and professional development.

The theme of leadership across generations was brought to life through reflections from past PSSA Presidents: Dr Johann Kruger, Prof Sarel Malan, Mr Tshifhiwa Rabali, and pre-recorded messages from Mr Joggie Hattingh and Dr Sybil Seoka. Their contributions provided a rich historical perspective, emphasising the continuity of leadership and the enduring values that have guided the Society over the years. These reflections served as a reminder that the strength of the PSSA lies in its ability to build on the legacy of its leaders while embracing new ideas and perspectives.

Adding a creative dimension to the programme, an artistic poetry performance offered a sentimental reflection on the role of pharmacists as custodians not only of medicines but also of health, advocates for patients, and contributors to society. This segment captured the human element of the profession, reminding attendees of the compassion and dedication that underpin pharmaceutical practice.

As the celebration drew to a close, it was evident that the 80th anniversary of the PSSA was not merely a commemoration of the past, but a call to action for the future. The event highlighted the importance of strengthening partnerships between academia, industry, regulators, and practitioners, while also creating space for emerging voices within the profession.

The PSSA's journey over the past 80 years is a testament to the resilience and adaptability of the pharmacy profession in South Africa. From its early beginnings to its current role as a unifying body representing diverse sectors, the Society has consistently championed the interests of pharmacists and the patients they serve. As the healthcare landscape continues to evolve, the PSSA remains well-positioned to lead the profession into the future.

In celebrating this milestone, the PSSA reaffirms its commitment to its core mission: To support and promote the pharmacy profession in advancing patient care and providing medicine access to all by harnessing professional standards of pharmaceutical practice in all settings. The 80th anniversary serves as both a reflection of past achievements and a foundation upon which the future of pharmacy can be built.

Delegates attending PSSA's 80th celebration

Plenary Session 2 on the PSSA SAPHEX programme featured a panel discussion on the National Health Insurance (NHI) and its implications for pharmacy. The opening presentation by the session Chairperson, Dr Sham Moodley, outlined NHI milestones, current progress, and the implications for pharmacy services, setting the context for the broader discussion. Central to the conversation was how medicines would be managed within the NHI framework, including their selection, pricing, procurement or reimbursement, and the contracting of both public and private pharmacies.

From a policy standpoint and health economics perspective, presented by Prof Nicholas Crisp, provided insight into the direction of NHI implementation and addressed considerations of sustainability and cost-effectiveness within the system. The private sector viewpoint, shared by Mr Jameel Kariem of the South African Association of Community Pharmacists, focused on implementation readiness and the preparedness of community pharmacies. From the public sector, Mr Nhlanhla Mafarafara of the South African Association of Hospital and Institutional Pharmacists spoke to system alignment and the realities within public healthcare settings.

Panel discussion on NHI

A key starting point was the legal status of the NHI Act. It was clarified that while certain sections of the Act have been paused by agreement and made an order of court, this does not constitute a final ruling on its constitutionality. Importantly, preparatory work has not been halted, and government continues to advance key elements of system readiness while awaiting the outcome of Constitutional Court proceedings. In this context, it was emphasised that NHI preparation is ongoing and cannot be delayed. Efforts are continuing across multiple areas, including health system strengthening, improvements to hospitals and clinics, medicine supply systems, stock visibility, digital health infrastructure, patient registration systems, provider accreditation design, and benefit package development. The overarching message was that system readiness must progress in parallel with legal processes.

The discussion further highlighted that NHI implementation will be phased rather than immediate, with primary healthcare expected to form the foundation of early rollout. This phased approach reflects a deliberate strategy to introduce reforms progressively, allowing for system adjustment and learning over time. Within this evolving framework, pharmacy was consistently positioned as central to the future health system. Panellists emphasised that pharmacists are expected to play a broad and integrated role spanning manufacturing, distribution, hospital and community pharmacy, dispensing, patient counselling, and preventive and clinical services. There was a clear long-term vision of pharmacists functioning as part of multidisciplinary primary healthcare teams, contributing to improved access, continuity of care, and patient convenience.

From a private sector perspective, community pharmacy was described as willing and capable, but not uniformly ready. While many pharmacies already provide services such as blood pressure and glucose monitoring, screening, and basic patient support, gaps remain in clinical capability, training, accreditation readiness, information technology systems, staffing, infrastructure, and operational funding. Differences in readiness between corporate and independent pharmacies were noted as a significant consideration. The issue of accreditation under NHI was also clarified. It was indicated that pharmacies are unlikely to face entirely new or duplicative inspection processes, given existing regulation by the South African Pharmacy Council. Instead, a streamlined process involving application and submission of compliance documentation is anticipated, with the stated intention of expanding access rather than limiting participation.

From the public sector perspective, the discussion acknowledged that South Africa has developed strong national policies and systems relating to medicine selection, essential medicines lists, procurement, and pricing. However, a consistent concern was the gap between national design and provincial implementation, with variability in execution at facility level remaining a major challenge. Concerns around procurement and supply chain systems featured prominently. It was noted that current approaches often rely on historical consumption rather than actual patient need, limiting the system's ability to accurately forecast demand and ensure continuity of care. A shift toward data-driven planning based on patient numbers, disease burden, adherence, and treatment outcomes was identified as essential for improving procurement, reducing waste, and strengthening service delivery.

A key structural concept discussed was the purchaser–provider split. Under this model, the NHI Fund will act as a strategic purchaser, responsible for funding services, determining benefits and formularies, and contracting providers, while not directly delivering care. Providers, including pharmacies, would remain responsible for procuring, stocking, and dispensing medicines, with reimbursement aligned to the NHI payment framework. This positions pharmacies as potential key access points for publicly funded medicine distribution. The continued use of Essential Medicines Lists and Standard Treatment Guidelines was anticipated, with increasing support from Health Technology Assessment to guide decisions on cost-effectiveness, value for money, and benefit design. However, pharmacy reimbursement models remain unresolved. Various options, including capitation, fee-for-service, and blended approaches, were discussed, with recognition that a single model may not be suitable across diverse practice settings. The potential inclusion of performance-based incentives linked to quality and outcomes was also raised.

One of the most consistent themes throughout the discussion was the limitation of current information systems. The health system was described as fragmented and heavily reliant on paper-based processes, resulting in poor continuity of care, weak medicine tracking, and limited ability to plan effectively. The proposed digital future includes integrated systems such as a national patient registration system, provider registries, a master facility list, and electronic medical records, all aimed at improving data visibility, accountability, and coordination of care. This digital transition represents a significant operational shift for pharmacy. Panellists emphasised that readiness under NHI will depend not only on service provision but also on the ability of pharmacies to integrate with national digital systems, support stock visibility, and undertake structured clinical reporting. Pharmacists may be required to document patient interactions, interventions, and outcomes more consistently to support funding, quality measurement, and system planning.

Industry participants raised concerns regarding the sustainability of originator products, the need to diversify into generics, and the broader impact of NHI on local manufacturing. Government indicated that procurement strategies would aim to maintain supply stability by avoiding over-reliance on single suppliers. At the same time, local manufacturing was recognised as a strategic priority, with ongoing efforts to support domestic production capacity and regional collaboration.

The session concluded with a clear call to action for the pharmacy profession. Panellists emphasised the importance of continued engagement with policy processes, investment in technology, workforce upskilling, and the standardisation and expansion of services. Pharmacists were encouraged not only to respond to

policy developments but to actively shape them by proposing practical models, piloting solutions, and demonstrating the value of pharmacy within the health system. A particularly strong closing message was that pharmacy should move beyond asking what its role will be under NHI and instead define and demonstrate that role. The discussion underscored that while NHI presents uncertainty, it also offers a significant opportunity for the profession to position itself as a central contributor to universal health coverage in South Africa.

PSSA/INSIGHT CPD programme

Module 2: Obesity and weight loss in adults

Obesity can no longer be regarded as a condition caused simply by an imbalance between energy in and energy out and, by implication, something that can be managed by mere willpower. Clinical practice guidelines all over the world now acknowledge that obesity is a chronic disease, much like type 2 diabetes, hypertension and dyslipidaemia are chronic diseases.

Obesity is also associated with a higher risk of type 2 diabetes, cardiovascular disease and several cancers. Health-related quality of life is significantly lower for people living with obesity compared with the general population owing to impaired mental health, increased depression and anxiety, greater pain and discomfort and reduced mobility.

Many healthcare providers believe that obesity is the result of poor lifestyle choices that are under the voluntary control of affected individuals. However, many factors contribute to the development of obesity, including genetics, age, lifestyle factors, and hormonal issues.

This module provides an update on adult obesity, its prevention and management and is largely based on the recently published clinical practice guideline on the management of obesity in adults in South Africa.

PSSA/INSIGHT pharmacy staff clinical education programme

Module 2: Overweight and obesity

Overweight and obesity have increased globally. In 2022, an estimated 2.5 billion adults aged 18 years and older were overweight or obese. This corresponds to 43 % of adults aged 18 years and older being overweight or obese. This is a substantial increase from 1990, when 25 % of adults aged 18 years and older were overweight or obese.

Obesity is a chronic medical condition, much like type 2 diabetes and high blood pressure are chronic medical conditions. In other words, obesity can no longer be regarded as a condition caused simply by eating too much and exercising too little. This outdated perception has led to the stigmatisation of people living with obesity. We now know that there are many factors that contribute to the development of obesity, including genetics, age, and lifestyle factors.

This module is designed to equip pharmacy front shop staff to identify and refer customers who would benefit from weight loss interventions, particularly those looking for information on weight loss or wanting to purchase a weight-loss product.

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For more information or any registration queries, please contact our CPD Manager:

Glynis van der Watt

Tel: 011 706 6939

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Email: glynisv@insightmed.co.za

When relevance outshines timing – Reflections from SAPHEX 2026

Thinavhuyo Musekene

YPG presenters at SAPHEX: Telicia Jobraj, Matladi Morapedi, Aisha Adam and Kevin Baloyi

At SAPHEX 2026, the Young Pharmacists Group (YPG) delivered a compelling reminder that influence within the profession is not dictated by programme placement, but by purpose. Scheduled as the final session on a rain-soaked afternoon, the YPG could easily have been overlooked. Instead, it became one of the most engaging and thought-provoking sessions of the event.

This moment reflects a broader shift within pharmacy: young professionals are no longer waiting to be invited into conversations about the future, they are actively shaping them.

What made the session particularly impactful was not only the diversity of topics, but the coherence of its underlying message. Across discussions on mentorship, digital health, and generational dynamics, a clear theme emerged: the future of pharmacy will depend on how intentionally the profession invests in people, adapts to change, and fosters collaboration.

Mentorship, often spoken about but inconsistently implemented, stood out as a critical point of reflection. Framing mentorship as a "ripple effect" challenges the profession to move beyond passive encouragement toward active participation. If one empowered individual can influence many others, then mentorship is not simply a professional courtesy it is a strategic imperative.

Yet, this raises an uncomfortable question: are we doing enough to institutionalise mentorship within pharmacy? Too often, mentorship depends on informal relationships or individual initiative. While these are valuable, they are not sufficient. A profession that recognises the importance of mentorship must also take responsibility for creating structured, accessible, and inclusive mentorship opportunities.

The discussion on digital health further underscored the urgency of adaptation. As healthcare systems become increasingly digitised, pharmacists must reconsider the boundaries of their roles. Digital health promotion is no longer a niche interest, it is an essential component of modern healthcare delivery.

The call for pharmacists to become digital health champions is both timely and necessary. Whether through social media engagement, community-based interventions, or technology-driven patient support, pharmacists have an opportunity to extend their impact far beyond the dispensary. However, this opportunity also comes with responsibility. If pharmacists do not actively define their place in the digital health landscape, they risk being sidelined as other professions and sectors take the lead.

Equally significant was the conversation around generational dynamics within the profession. The perceived divide between younger and more experienced pharmacists is often framed as a tension between innovation and tradition. This framing, however, is overly simplistic and ultimately counterproductive.

Young pharmacists are navigating a professional environment characterised by systemic challenges, including limited opportunities, evolving practice demands, and increasing expectations. At the same time, experienced professionals hold the institutional knowledge and influence necessary to drive meaningful change. The issue, therefore, is not one of opposition, but of integration.

Progress within pharmacy will depend on the ability of these groups to move beyond assumptions and engage in genuine collaboration. This requires effort on both sides: younger professionals must be willing to learn and engage constructively,

while established practitioners must remain open to new perspectives and approaches.

Importantly, the session also highlighted the need for African voices in global health leadership. Encouraging young pharmacists to take up leadership roles is not merely aspirational; it is essential for ensuring that health systems are shaped by those who understand local contexts and challenges. Representation in leadership is not just about visibility it is about influence and impact.

The closing discussions reinforced a central idea: leadership in pharmacy is not confined to titles or positions. It is demonstrated through initiative, engagement, and a willingness to contribute to the profession's growth.

In many ways, the YPG session at SAPHEX served as both a reflection and a call to action. It highlighted existing strengths within the profession while also drawing attention to areas requiring deliberate focus and investment.

If there is one lesson to be taken forward, it is that the future of pharmacy will not be shaped by circumstance alone. It will be shaped by the choices made today by individuals who choose to mentor, to innovate, and to collaborate.

The question is no longer whether young pharmacists are ready to lead. The real question is whether the profession is prepared to evolve alongside them.

Bridging the gap before it widens – The promise of "Connect and Elevate"

Thinavhuyo Musekene

The journey from pharmacy student to practicing professional is often marked by a significant and persistent gap. While academic training provides the scientific and technical foundation required for practice, it frequently falls short in preparing students for the realities of the professional environment. This disconnect between knowledge and application, expectation and experience has long been recognised, yet remains insufficiently addressed.

The Young Pharmacists' Group (YPG), through its "Connect and Elevate" Campus Outreach Project, offers a timely and necessary intervention. More than a simple outreach initiative, it represents a rethinking of how the profession supports its future members.

At its core, "Connect and Elevate" is built on a powerful premise: Exposure shapes aspiration. By bringing together professionals from across the pharmacy landscape – including industry leaders, entrepreneurs, hospital pharmacists, and academics – the initiative provides students with access to perspectives that extend beyond the classroom.

This exposure is not merely informative; it is transformative. When students are able to engage with diverse career pathways and hear directly from those navigating them, they gain a clearer sense of what is possible. Career decisions become more intentional, and professional identity begins to take shape earlier.

This raises an important consideration for the profession: should career clarity be left to develop organically, or should it be actively cultivated? "Connect and Elevate" argues for the latter. It positions mentorship, guidance, and real-world engagement as essential components of professional development not optional extras.

The significance of this approach becomes even more apparent when considering the rapidly evolving nature of pharmacy. The profession is no longer confined to traditional roles, and career pathways are becoming increasingly diverse. Without adequate exposure, students may remain unaware of opportunities that align with their interests and strengths.

In this context, "Connect and Elevate" serves as a bridge that links academic training with professional reality. It helps to contextualise learning, making it more relevant and applicable. More importantly, it empowers students to navigate their careers with greater confidence and agency.

There is also an important equity dimension to the initiative. Access to mentorship and professional networks is not evenly distributed. Some students benefit from established connections and support systems, while others must navigate the profession with limited guidance. This disparity can influence not only career outcomes, but also confidence and participation within the profession.

By creating structured opportunities for engagement, "Connect and Elevate" has the potential to level this playing field. It ensures that exposure is not dependent on personal networks, but is made accessible to a broader group of students.

However, the success of such an initiative cannot be measured solely by its immediate impact. The true value lies in its sustainability and scalability. For "Connect and Elevate" to fulfil its potential, it must evolve into a continuous and widely accessible platform.

This will require collaboration across the profession. Academic institutions, professional bodies, and industry stakeholders all have a role to play in supporting and expanding such initiatives. Investment in early career development should not be seen as an added responsibility, but as a strategic priority.

Furthermore, initiatives like "Connect and Elevate" challenge the profession to reconsider how it defines preparedness. Academic competence, while essential, is only one aspect of professional readiness. Confidence, adaptability and awareness of opportunities are equally important, and these are often developed through exposure and engagement.

In this sense, "Connect and Elevate" represents more than a project; it signals a shift in mindset. It reflects a growing recognition that preparing future pharmacists requires a more holistic approach, one that integrates knowledge with experience, and ambition with guidance.

If sustained and expanded, this initiative could fundamentally reshape how students transition into the profession. Instead of entering the workforce uncertain and reactive, graduates could emerge informed, connected, and proactive.

Ultimately, the question is not whether initiatives like "Connect and Elevate" are valuable, their importance is clear. The real question is whether the profession is willing to invest in them long enough, and broadly enough, to create lasting change.

Because bridging the gap is not a once-off effort. It is an ongoing commitment.

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

Dry eye disease management: the pharmacist as first-line health professional

E Owusu, P Chinodyanama, E Bronkhorst

School of Pharmacy, Department of Clinical Pharmacy, Sefako Makgatho Health Sciences University, South Africa

Corresponding author, email: elmien.bronkhorst@smu.ac.za

Abstract

Dry eye disease is a disorder of the ocular surface, characterised by tear film instability, hyperosmolarity, inflammation, and neurosensory abnormalities. It is caused by multiple intrinsic and extrinsic factors that disrupt tear film stability and ocular surface homeostasis, from medication, environmental factors and use of contact lenses. Dry eye disease is diagnosed with the presence of symptoms as well as objective diagnostic tests. Patients commonly report dryness, burning, stinging, grittiness, and fluctuating or blurred vision. Treatment focuses on improving tear film stability and relieving symptoms. Eye drop formulations known as artificial tears are the mainstay treatment, which work by reducing inflammation and improving lubrication. The length of therapy varies and is dependent on the severity of symptoms, with acute symptoms treated for 3–14 days and chronic symptoms often for 1 month or more. Alternative therapies like topical corticosteroids, non-steroidal anti-inflammatory or vitamin A drops are indicated for more severe or chronic symptoms. Furthermore, medical device or surgical intervention may be considered. With most of the first-line treatment available as over-the-counter products, pharmacists are often the first point of contact when seeking healthcare, and pharmacists must be able to differentiate between dry eye disease and other ophthalmic conditions and know when to refer for further specialist follow-up.

Keywords: dry eye disease, tear film instability, artificial tears, pharmacist-initiation

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Introduction

Dry eye disease (DED) is a common disorder of the ocular surface that is characterised by tear film instability, hyperosmolarity, inflammation, and neurosensory abnormalities.[1] It is not just a simple deficiency of tears but a chronic inflammatory condition that affects the ocular surface and lacrimal function. As illustrated in Figure 1, the tear film consists of lipid, aqueous, and mucin layers that help maintain optical clarity, lubrication, and protect the cornea. If any component of this structure is compromised, there is loss of ocular surface integrity that may lead to visual function impairment.[2]

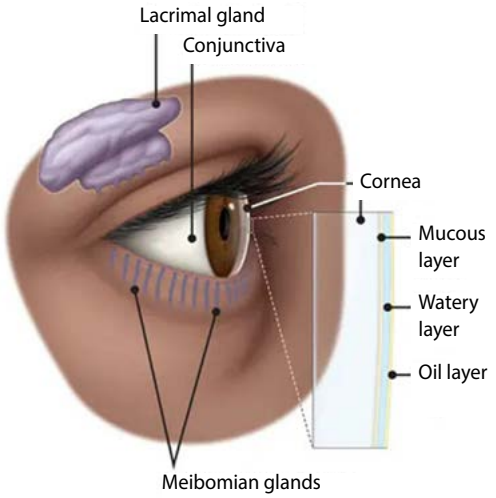

Figure 1: Anatomy of the tear film showing its three major layers – lipid, aqueous and mucin – covering the ocular surface[5]

DED is classified into two major types – aqueous tear deficiency and evaporative dry eye, with most patients presenting with features of both types.[1] Aqueous tear deficiency is caused by reduced lacrimal gland secretion, which leads to inadequate tear volume. Evaporative dry eye occurs when excessive tear evaporation due to meibomian gland dysfunction destabilises the tear film.[3] Evaporative dry eye is the most prevalent type globally, especially due to prolonged digital screen use, environmental dryness, or incomplete blinking.[4]

Globally, the prevalence of DED differs depending on the diagnostic criteria and study population, reported to range from approximately 5% to more than 50%.[4] A recent systematic review and meta-analysis by Ismail et al.[6] of 15 studies involving over 7 000 participants reported an overall prevalence of approximately 43.6%, ranging from about 30.7% in some African regions to over 80% in South Africa. This highlights that nearly four in ten individuals in African settings are affected by DED, underscoring its significance as a public health concern. Similarly, South African studies showed a high prevalence that is influenced by environmental factors, occupational exposure, climate, and comorbidities such as diabetes mellitus.[7] DED significantly impairs quality of life, reduces productivity, and causes economic and healthcare burden, particularly in the older population.[8]

Aetiology

DED is caused by multiple intrinsic and extrinsic factors that disrupt tear film stability and ocular surface homeostasis. Aqueous tear deficiency may be caused by autoimmune destruction of the

lacrimal gland in Sjögren's syndrome, or from age-related lacrimal gland dysfunction and systemic diseases such as diabetes mellitus.[3] Certain medications such as antihistamines, antidepressants, and isotretinoin reduce tear secretion through anticholinergic effects and suppressing the lacrimal gland.

Evaporative dry eye is secondary to meibomian gland dysfunction, where there is obstruction or altered lipid secretion that reduces stability of the tear film's lipid layer.[1] The function of the lipid layer is to prevent excessive evaporation; its dysfunction accelerates tear film breakup and increases osmotic stress on the ocular surface. Air pollution, low humidity, high temperatures, and prolonged screen exposure increase the rate of evaporation. Epidemiological studies also identify increasing age, the female sex, hormonal influences, use of contact lenses, and systematic inflammation as risk factors.[4,9] In South African populations, rising temperatures, intense heat, and dry conditions combined with occupational exposures, such as outdoor manual labour in agriculture, mining, and construction and indoor work in poorly ventilated or environments with no air-conditioning, may amplify susceptibility to evaporative mechanisms.[7,10]

Pathophysiology of dry eye disease

DED results from the disruption of tear film homeostasis and inflammation. Reduced tear production and increased evaporation lead to tear hyperosmolarity, which is the key mechanism of the disease.[1] Hyperosmolar tears cause osmotic stress on the epithelial cells of the cornea and conjunctiva, which triggers intracellular signalling cascades that promote the release of pro-inflammatory cytokines and matrix metalloproteinases.[3]

The inflammatory response results in epithelial cell damage, loss of goblet cells, and decreased mucin production, further destabilising the tear film. Goblet cells secrete mucins that allow tears to adhere to the ocular surface. Loss of goblet cells compromises the integrity of the tear film and accelerates tear breakup. Chronic inflammation may impair lacrimal gland function, further reducing aqueous tear production and intensifying hyperosmolarity. Recent immunobiological research further highlights the role of both innate and adaptive immune responses in sustaining inflammation, including T-cell activation and cytokine-mediated tissue damage.[11]

All these mechanisms interplaying simultaneously cause a self-perpetuating cycle of DED, where tear instability, hyperosmolarity, and inflammation lead to chronic damage of the ocular surface and persisting symptoms.[1] Neurosensory abnormalities may develop, altering corneal nerve function and contributing to symptom-sign discordance observed in many patients.[12]

Diagnostic parameters

DED diagnosis requires both the presence of symptoms and objective evidence of tear film instability or ocular surface damage.[1] Standardised symptom questionnaires, such as the Ocular Surface Disease Index (OSDI) and the Dry Eye Questionnaire (DEQ-5), are typically used to determine symptom intensity and effect on daily activities.[4]

Objective diagnostic tests assess tear production, stability, and osmolarity. Tear break-up time (TBUT) evaluates tear film stability. It is a measure of duration from a complete blink to the first visible dry spot on the corneal surface.[13] It is commonly measured using fluorescein dye that is applied into the lower conjunctival sac using a moistened strip; the patient is asked to blink to distribute the dye evenly across the tear film and then avoid blinking while keeping the eyes open.[14] A slit lamp with cobalt blue filter is used to measure the interval (in seconds) from the last blink to the first dark spot on the cornea, indicating tear film break-up.[14] The test is typically repeated and averaged, and a value of less than 10 seconds suggests tear instability.[15] The Schirmer test measures aqueous tear production, where a narrow strip of filter paper is inserted inside the lower eyelid for 5 minutes, and the extent of wetting indicates tear secretion: 0–5 mm indicates extremely dry eyes, 5–10 mm moderately dry, 10–15 mm possible dry eyes, and over 15 mm is considered normal.[16] Tear osmolarity testing provides a quantitative marker of hyperosmolar stress, with values ≥ 308 mOsm/L or significant inter-eye differences supporting a diagnosis of dry eye.[1] Ocular surface staining with fluorescein or lissamine green enables visualisation of epithelial damage and is useful in grading disease severity.[17]

Contemporary diagnostic approaches emphasise combining symptom assessment with multiple objective parameters rather than relying on a single test, thereby improving diagnostic accuracy and allowing for subtype differentiation.[9]

Signs and symptoms

Symptoms are characteristic of tear film instability and ocular surface irritation. Patients commonly report dryness, burning, stinging, grittiness, and fluctuating or blurred vision. Visual disturbances worsen when there is reduced blinking during prolonged computer use or reading.[4] In some cases, excessive reflex tearing may occur due to ocular surface irritation.

Clinical signs may include reduced TBUT that is normally ≥ 10 seconds, where a TBUT of < 5 seconds indicates moderate to severe dry eye; bright red and green spots after corneal and conjunctival epithelial staining with fluorescein or lissamine green; conjunctival hyperaemia; and evidence of meibomian gland dysfunction.[3] Reduced Schirmer test values may indicate aqueous deficiency. Importantly, numerous studies highlight a poor correlation between symptoms and clinical signs, suggesting that neurosensory changes and central pain mechanisms may contribute to patient-reported severity.[1]

Pharmacological therapy of dry eye syndrome

The treatment and management of dry eye syndrome (DES) focus on improving tear film stability and relieving symptoms. Eye drop formulations known as artificial tears are the mainstay treatment for dry eyes and work by reducing inflammation and improving lubrication.

Table I: Types of artificial tears

Types of artificial tears	Mechanism of action	Indications	Side effects
Lubricants e.g. Allergan® Refresh Tears Lubricating Eye Drops	Reduce evaporation and increase the thickness of the tear film.	First-line treatment of mild to moderate dry eye disease.	Temporary: blurred vision, discomfort, burning, itchiness, and crusting of the eyelids.
Electrolytes e.g. Allergan® Optive Plus Eye Drops	It contains osmo-protectants that maintain tear film osmolarity and ocular surface homeostasis.	1) Mild to moderate dry eye. 2) Dry eye disease caused by environmental factors, e.g., wind and dust.	Temporary: blurred vision, itchiness, burning and discomfort, and an unpleasant taste in the mouth. Rare allergies.
Lipid-based and surfactant formulations e.g. Artelac® Advance Lipids Eye Drops	Replenishes the deficient lipid layer to prevent tear evaporation.	1) Meibomian gland dysfunction 2) Severe dry eye disease	Temporary blurred vision, conjunctival redness, and rare allergies.
Preservative-free formulations e.g., Systane® Ultra Lubricant Eye Drops	Recommended for patients with sensitive eyes and requiring frequent application. Some preservatives can irritate the eyes, particularly in severe dry eye cases	Mild to moderate dry eyes caused by environmental factors, e.g., wind and dust, for sensitive eyes.	Less side-effects because of preservative irritation

The length of therapy of these formulations varies and is dependent on the severity of the dry eye symptoms. Acute symptoms are treated for 3 days to 2 weeks and chronic symptoms for 1 month or more. Types of artificial tear formulations are presented in Table I.[18,19]

Eye drop formulations are also available as gel formulations, especially those that are electrolyte-based. Gel formulations are preferred for moderate to severe dry eye conditions. They have higher viscosity and have increased retention on the site of application, providing longer-lasting lubrication and protection.[20]

Topical non-steroidal anti-inflammatory drugs (NSAIDs) are used to treat DED, as they work to relieve the symptoms of DES by effectively stimulating the secretion of tears. Examples are pranoprofen and sodium hyaluronate formulations. Topical NSAIDs formulations that contain antibiotics are commonly used for the treatment of meibomian gland dysfunction are not recommended for patients with mild DED.[21]

Topical corticosteroids are effective in the treatment of moderate-to-severe DED for 2–4 weeks. Examples are prednisolone, fluorometholone, dexamethasone, and loteprednol etabonate.[21] Topical cyclosporine, an immunosuppressant, is also used to manage ocular surface inflammation of moderate-to-severe DED. Cyclosporine A requires a longer period to become effective in controlling inflammation.[21]

Topical vitamin A drops are used for DED to protect the eye from toxins, inflammation, and allergens. It is naturally present in the tear film of healthy eyes and plays a pivotal role in the production of the mucin layer, which is the innermost layer of the tear film. Vitamin A deficiency leads to mucin layer loss, which is crucial for a healthy tear film.[21]

Autologous and allogeneic serum eye drops (SEDs) are an alternative treatment option for dry eye cases that do not respond to artificial tear formulations. These are eye drops that contain natural serum and electrolytes. SEDs are prepared when autologous or allogeneic whole blood is collected without anticoagulant. This blood is then allowed to clot, and the serum is separated and collected after centrifuging the clotted blood in a closed system. The serum is diluted in physiological saline using aseptic techniques and dispensed in small aliquots for daily use. SEDs are stored frozen following preparation.[22] This serum contains electrolytes like those found in natural tears and provides key tear-like components such as vitamins and proteins that have electrolytes for osmolarity and pH balance that match healthy tears.[22]

Autologous drops deliver bioactive electrolytes and factors that promote epithelial healing in severe dry eye cases. They act by reducing inflammation and supporting goblet cells, beyond mere lubrication.[22]

Non-pharmacological therapy for dry eye management

Patients with dry eye symptoms can minimise their discomfort through appropriate precautions and lifestyle changes, such as;[18]

- Reduce screen time (computer screens and phones) and reduce brightness levels to appropriate settings.
- When using a computer for extended periods, take regular breaks to rest and blink your eyes.
- Avoid contact lenses, as they constantly irritate the eyes. If it is absolutely necessary, be sure to clean them regularly.
- Reduce smoking, as it can increase symptoms.
- Use a humidifier to moisten the ambient air
- Avoid dry and windy environments, as they can exacerbate symptoms, or wear wraparound sunglasses.
- Stay hydrated to support tear production.
- Avoid medications that may cause or exacerbate dry eye symptoms, e.g., antihistamines and antidepressants.
- Use warm eye compresses and lid scrubs to enhance oil flow from the meibomian glands and alleviate dry eye symptoms like grittiness and burning.

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References: 1. Artelac® Complete XP Eye Drops, instructions for use, I999EU-07;2024-08. **2.** Artelac® Advanced Lipids Eye Drops, instructions for use, I174EU-06;2023-06. **3.** Artelac® Advanced Lipids Eye Lubricant Drops (UD), instructions for use, I168EU-03; 2023-06. **4.** Artelac® Advanced Lipids Eye Gel, instructions for use, I174EU-06; 2023-06. **5.** Artelac® Intense Rebalance Eye Drops, instructions for use, I781EU-08-Milan;2024-09. **6.** Artelac® Splash Eye Drops, instructions for use, I931EU-06;2023-06. **7.** Artelac® Moisture Eye Drops, instructions for use, I188EU-04;2024-08. **8.** Artelac® Allergy Eye Drops, instructions for use, I228EU-04;2024-08. **9.** Artelac™ Ultra 4S Eye Drops, Instructions for Use. 2025-08

Proprietary name: Artelac® Complete XP Eye Drops. Contains: 0,24 % sodium hyaluronate, carbomer, glycerol, lipid component (medium chain triglycerides). Preservative free. **Proprietary name:** Artelac® Advanced Lipids Eye Drops. Contains: 2 mg carbomer, medium chain triglycerides. Preservative: Cetrimide. **Proprietary name:** Artelac® Advanced Lipids Eye Lubricant Drops (UD). Contains: 2 mg carbomer, medium chain triglycerides. Preservative free. **Proprietary name:** Artelac® Advanced Lipids Eye Gel. Contains: 2 mg carbomer, medium chain triglycerides. Preservative: Cetrimide. **Proprietary name:** Artelac® Intense Rebalance Eye Drops. Contains: 0,15 % hyaluronic acid (as sodium hyaluronate), 0,5 % polyethylene glycol 8000, potassium chloride, calcium chloride, magnesium chloride, sodium chloride, vitamin B12. Preservative: Oxyd® (a gentle preservative that converts to water, oxygen and salt at the surface of the eye). **Proprietary name:** Artelac® Splash Eye Drops. Contains: 0,24 % hyaluronic acid (as sodium hyaluronate). Preservative free. **Proprietary name:** Artelac® Moisture Eye Drops. Contains: 0,32 % hypromellose. Preservative: Cetrimide. **Proprietary name:** Artelac® Allergy Eye Drops. Contains: 0,24 % hyaluronic acid (as sodium hyaluronate), 2 % Ectoin®. Preservative free. **Proprietary name:** Artelac™ Ultra 4S. Contains: 0,15 % sodium hyaluronate, 3 % trehalose, 0,1 % fucoidan, 2 % D-panthenol. Preservative free.

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Medical devices are used to treat dry eye symptoms after medications and lifestyle modifications fail. Devices used in the management and treatment include:

1. Tixel® uses Thermal-Mechanical Action technology (TMA®), this device employs a medical-grade titanium applicator to deliver controlled thermal energy in a fractional, non-laser manner. Heat is applied through an array of microscopic, pyramid-shaped projections composed of biocompatible material, treating a surface area of approximately 0.3 cm^2 per application. By thermally stimulating periocular tissues, the procedure aims to improve tear film stability, enhance lubrication, and decrease evaporative loss. It is a non-invasive treatment that can naturally enhance moisture levels and restore hydration to the eyes.[23]
2. E-Eye IRPL uses Intense Regulated Pulsed Light (IRPL) and is a non-invasive treatment for Meibomian Gland Dysfunction (MGD). This method works by generating polychromatic pulsed light, delivering precisely calibrated pulses that are homogenous, controlled, and delivered in a sequenced pattern. These pulses stimulate the meibomian glands, helping them return to normal lipid secretion and restoring the tear film's stability. This process works within hours; the meibomian glands are reactivated, significantly improving tear quality and reducing symptoms like dryness, burning, blurry vision, and eye fatigue.[24]
3. Punctal Plugs (Figure 2) are tiny silicone or gel plugs inserted into the tear ducts to retain the natural tears in the eye and prolong their stay in the eyes. These are reversible and can be removed when indicated.

Surgical interventions are the last step in the treatment and management of DED and are used when pharmacological therapy, lifestyle modifications, and medical devices fail.

Surgical interventions performed include:

1. Tarsorrhaphy eye surgery - a surgical procedure where the eyelids are partially sewn together to reduce eyelid separation and protect the cornea from exposure, which in turn helps to reduce tear evaporation. By limiting the cornea from exposure, it creates a stable, moist environment that promotes epithelial recovery and prevents moisture loss.[26]
2. Amniotic membrane grafting - a procedure that uses a cryopreserved amniotic membrane graft to promote healing, reduce inflammation, minimise scarring, and stimulate tissue regeneration. The amniotic membrane is the innermost membrane of the placenta, and it is rich in bioactive substances, including growth factors and cytokines, which play a vital role in foetal development. When applied to the ocular surface, the amniotic membrane promotes wound healing, modulates inflammation and may assist with pain reduction at the affected site. The membrane is placed over the cornea like a "bandage." It is a minimally invasive, in-office procedure where the tissue is secured by a ring or bandage contact lens.[26]
3. Punctal cautery - an in-office surgical procedure that uses a thermal cautery – a fine-tip heated device – to permanently close the puncta (tear drainage openings in the eyelids). This prevents tears from draining away too quickly and prolongs moisture on the ocular surface. This procedure scars the canaliculi to block drainage without plugs and is preferred over plugs.[26]

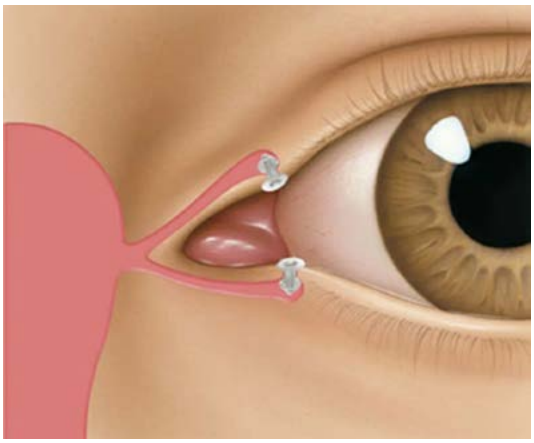

Figure 2: A punctual plug being inserted into the tear duct[25]

Role of the pharmacist

The scope of practice of pharmacists has broadened considerably over the years, increasing access to care and improving patient health outcomes.

At the local pharmacy level, pharmacists play a crucial role in recognising symptoms and differentiating between allergies and dry eye disease to recommend the appropriate treatment. As first-line treatment is available as over the counter products, pharmacists are often the first-line healthcare-contact with patients. Allergic patients often present with swollen and puffy eyelids with an intense red conjunctiva and clear watery discharge, which the pharmacist should be able to differentiate. Dry eye patients present with normal eyelids with crusty margins, no conjunctival redness, and stringy mucus-like discharge.[27]

Pharmacists improve patient care by referring the patient when the treatment fails, symptoms become severe, and there are complications. Pharmacists must educate the patient on pharmacological and non-pharmacological DED management strategies and the medical devices available to treat and manage DED.[18]

Conclusion

DED is a condition that is prevalent in up to 80% of patients in some regions of South Africa. It can be treated easily with over-the-counter preparations called artificial tears. The treatment varies from between 1–14 days in acute conditions, to one month or more in chronic symptoms. It involves replenishing the tear film and lacrimation to improve the ocular surface area. The pharmacist must be able to identify DED and differentiate from other ocular

diseases like allergic eye. The pharmacist can distinguish whether over the counter treatment will be beneficial, or if the patient should be referred for further healthcare treatment.

ORCID

E Bronkhorst https://orcid.org/0000-0002-6872-5417

References

1. Craig JP, Nichols KK, Akpek EK, et al. TFOS DEWS II Definition and Classification Report. Ocul Surf. 2017;15(3):276-83. https://doi.org/10.1016/j.jtos.2017.05.008.
2. Pflugfelder SC, Stern ME. Biological functions of tear film. Exp Eye Res. 2020;197:108115. https://doi.org/10.1016/j.exer.2020.108115.
3. Bron AJ, de Paiva CS, Chauhan SK, et al. TFOS DEWS II pathophysiology report. Ocul Surf. 2017;15(3):438-510. https://doi.org/10.1016/j.jtos.2017.05.011.
4. Stapleton F, Alves M, Bunya VY, et al. TFOS DEWS II Epidemiology Report. Ocul Surface. 2017;15(3):334-65. https://doi.org/10.1016/j.jtos.2017.05.003.
5. American Academy of Ophthalmology. (n.d.). Tear film anatomy illustration. Retrieved from: https://www.aao.org/eye-health/anatomy/tear-film-3.
6. Ismail MF, Khalafalla I, Qarbote AI. Prevalence of dry eye disease in African populations: A systematic review and meta-analysis. BMC Ophthalmol. 2025;25:508. https://doi.org/10.1186/s12886-025-04290-7.
7. Mefane TK. Prevalence and risk factors of dry eye disease in a South African population (Master's thesis). University of Limpopo; 2021.
8. Farrand KF, Stillman IÖ, Fridman M, Schaumberg DA. PSS30 - Impact of dry eye disease on quality of life, work productivity, daily activities, and health care resource use in a survey of 74 095 American adults [Abstract]. Value Health. 2016;19(3):A127.
9. Britten-Jones AC, Wang MTM, Samuels I, et al. Epidemiology and risk factors of dry eye disease: Considerations for clinical management. Medicina (Kaunas, Lithuania), 2024;60(9):1458. https://doi.org/10.3390/medicina60091458.
10. Kjellstrom T, Lemke B, Hyatt O, Otto M. Climate change and occupational health: A South African perspective. S Afr Med J. 2014;104:586. https://doi.org/10.7196/SAMJ.8646.
11. Saram SJ, Thomas MN, Feinberg L, et al. The immunobiology of dry eye disease: A review of the pathogenesis, regulation and therapeutic implications. Int J Mol Sci. 2025;26(21):10583. https://doi.org/10.3390/ijms262110583.
12. Kaštelan S, Kozina L, Tomić Z, et al. Dry eye disease and psychiatric disorders: Neuroimmune mechanisms and therapeutic perspectives. Int J Mol Sci. 2025;26(21):10699. https://doi.org/10.3390/ijms262110699.
13. Zhao S, Le Q. Analysis of the first tear film break-up point in Sjögren's syndrome and non-Sjögren's syndrome dry eye patients. BMC Ophthalmol. 2022;22(1):1. https://doi.org/10.1186/s12886-021-02233-6.
14. Galor A. Tear film and corneal diagnostic techniques. In: Mannis MJ, Holland EJ, editors. Cornea: Fundamentals, diagnosis and management. 5th ed. Elsevier; 2021. p. 81-7.
15. Golden MI, Meyer JJ, Zeppieri M, et al. Dry eye syndrome. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470411/.
16. Brott NR, Zeppieri M, Ronquillo Y. Schirmer test. In [Internet]. Treasure Island (FL): StatPearls Publishing; 2024. https://www.ncbi.nlm.nih.gov/books/NBK559159/.
17. Srinivas SP, Rao SK. Ocular surface staining: Current concepts and techniques. Indian J Ophthalmol. 2023;71(4):1080-9. https://doi.org/10.4103/ijo.IJO_2137_22.
18. Van Staden M. Dry eye disease: A comprehensive overview for pharmacists. SA Pharmaceutical Journal. 2024;91(5):14-7. https://doi.org/10.36303/SAPJ.0995.
19. Munde AA. Artificial tears for dry eye: A review. International Journal of Pharmaceutical Research and Applications. 2024;9(6):592602. https://doi.org/10.35629/4494-0906592602.
20. Semp DA, Beeson D, Sheppard AL, Dutta D, Wolffsohn JS. Artificial tears: A systematic review. Clin Optom. 2023;15:9-27. https://doi.org/10.2147/OPTO.S350185.
21. Mathebula SD, Mmusi-Landela L. Pathophysiology of dry eye disease and novel therapeutic agents. African Vision and Eye Health. 2024;83(1). https://doi.org/10.4102/aveh.v83i1.874.
22. Van der Meer PF, Verbakel SK, Honohan Á, et al. Allogeneic and autologous serum eye drops: A pilot double-blind randomized crossover trial. Acta Ophthalmol. 2021;99(8):837-42. https://doi.org/10.1111/aos.14788.
23. Sanni N, Koloms D, Case B, Bailey L. Tixel i®: Advancing management of evaporative dry eye with thermo-mechanical action®. JOJ Ophthalmol. 2025;12(4). https://doi.org/10.19080/JOJO.2025.12.555844.
24. Adcock L, Rennick S. Intense pulsed light therapy for meibomian gland dysfunction: A review of clinical effectiveness and guidelines [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2018. Available from: https://www.ncbi.nlm.nih.gov/books/NBK531789/ 2018.
25. Innovia Medical; 2026. Available from: https://innoviamedical.com/ophthalmic/p
26. Møller-Hansen M, Utheim TP, Heegaard S. Surgical procedures in the treatment of dry eye disease. J Ocul Pharmacol Ther. 2023;39(10):692-8. https://doi.org/10.1089/jop.2023.0063.
27. Lam D, Chong K, Shih K, Wan KH, Cheng A. Optimising diagnosis and management of dry eye disease: A practical framework for Hong Kong. Ophthalmol Ther. 2025;14(5):815-33. https://doi.org/10.1007/s40123-025-01129-8.

SILVERLAB

Advanced Immune Support: The Clinical Role of Ionic Silver in Winter Ailments

As the winter season approaches, pharmacies face an influx of patients presenting with upper respiratory tract infections, seasonal flu, and secondary bacterial complications. In this landscape, **Silverlab Healthcare's** ionic Silver (Ag^+) stands out as a versatile, science-backed tool for immune support and infection management.

Unlike generic colloidal silvers, Silverlab is a pharmaceutical-grade formulation consisting of ionic silver in purified, deionised water. For the pharmacist, this represents a non-toxic, broad-spectrum antimicrobial intervention with a validated safety and efficacy profile.

Potent Antiviral and Antibacterial Efficacy

Winter infections are primarily viral, often leading to secondary bacterial issues. Silverlab's efficacy against respiratory and systemic pathogens has been rigorously tested:

- SARS-CoV-2: Independent research demonstrated that the Silverlab formulation achieved a 4-log (99.99%) reduction in viral load within 60 seconds.
- Broad-Spectrum Bactericidal Action: Independent testing confirms rapid elimination (often under 30 seconds) of critical pathogens, including S. aureus, P. aeruginosa, E. coli, and V. cholerae.
- Avian Influenza: Our Recent 2026 data confirms high-threshold inhibition of the H5 subgroup, reinforcing its relevance against evolving viral strains.

Therapeutic Application: From Consumables to Nebulising

The **Silverlab Immune Booster** liquid offers a unique multimodal application for winter health:

Multi-modal Action: Beyond Antimicrobial

A common challenge in treating nasal congestion is the underlying inflammatory response. Silverlab's ionic silver provides additional therapeutic benefits:

- Oral Support: Systemic intake supports the body's natural defences. Multiple 28-day and 90-day oral toxicity studies confirmed that doses resulted in no clinical abnormalities or macro-pathology.
- Nebulising for Respiratory Health: For patients with lower respiratory tract concerns, Silverlab 'Immune Booster' 18 ppm liquid, as well as our 25 ppm 'nebulising liquid', can be nebulised. Inhalation toxicity tests showed that even intensive regimens simulated to mimic severe human treatment models resulted in no clinical signs of toxicity.
- Inflammatory modulation action: Chronic winter ailments often involve significant inflammation. In vitro assays confirmed that Silverlab can inhibit the pro-inflammatory cytokines IL-6/ TNF-α by a factor of 5 compared to control models.

A Benchmarked Safety Profile

Pharmacists can recommend Silverlab with confidence due to its extensive toxicological vetting:

- Cellular Safety: Assays in human lung (A549) and kidney cell lines showed no cytotoxicity (tested at an 18x normal-use strength), indicating the formulation is safe for therapeutic consideration.
- Purity & Stability: Silverlab products are free from stabilisers and carriers. Packaged in amber glass to maintain the integrity of the ionic silver throughout the product's shelf life.

The Pharmacist's Clinical Advantage

With a 4-log (99.99%) viral-reduction capability and a proven safety record across oral and inhalation routes, Silverlab ionic Silver is a modern clinical tool.
As we head into winter, it offers a dual-action approach: directly inhibiting a wide array of pathogens while modulating the inflammatory response, ensuring patients recover faster and remain protected.

Key Clinical Data points:

- 99.99% reduction of SARS-CoV-2 in 60 seconds.
- Non-cytotoxic to human lung and kidney cells.
- 97.4% ionic silver content for maximum bio-availability.
- 5x decrease in pro-inflammatory markers (IL-6/TNF-α).

Clients also love our stronger, 25 ppm Nebulising Liquid - available in a convenient 50ml bottle


Boost your clients immunity & shield their body naturally
✓ Immune System Support
✓ Cold & Flu (Anti-Viral) Support
✓ Anti-inflammatory Support
SILVERLAB
DAILY
IMMUNE BOOSTER
& ANTI-MICROBIAL
ionic+ Colloidal Silver
SILVERLAB
Taken daily, Silverlab Immune Booster can help strengthen the immune system and help fight infections. In ionic+ form, Silverlab's Immune Booster is proven to be more effective, yet is a natural trace mineral and has a favourable safety profile.
More info

Beyond energy boosts: a clinical review of the vitamin B complex and associated supplementation

M Naidoo, W Cordier

Department of Pharmacology, School of Medicine, Faculty of Health Sciences, University of Pretoria, South Africa
Corresponding author, email: werner.cordier@up.ac.za

Abstract

The vitamin B complex is a group of water-soluble vitamins composed of eight B vitamins: thiamine (B1), riboflavin (B2), niacin (B3), pantothenic acid (B5), pyridoxine (B6), biotin (B7), folate/folic acid (B9) and cobalamin (B12). Vitamins are crucial for optimal physiological functions, and thus adequate amounts of vitamins need to be supplied through the diet since they are not synthesised endogenously by the human body. Vitamin B deficiency may occur for a variety of reasons, and depending on the specific vitamin and its functions, symptoms may vary. Due to potential deficiencies, vitamin B supplements are considered to mitigate these effects. Available vitamin B supplementation ranges from Schedule 0 (over-the-counter) to Schedule 4 (scheduled preparations), in various formulations and routes of administration, however, specific dosages need to be considered to prevent toxicity. Vitamin B supplements are not only used for direct supplementation but also to support the function of pharmacotherapy or mitigate adverse drug reactions. This review provides a broad overview of the vitamin B complex, particularly its deficiencies, indications for supplementation, available supplements and potential drug-vitamin interactions.

Keywords: biotin, cobalamin, folate, niacin, pantothenic acid, pyridoxine, riboflavin, thiamine, vitamin B complex, vitamin B deficiency

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Introduction

Vitamins are a group of essential organic micronutrients, either water- or fat-soluble, required for normal physiological functioning but are not synthesised endogenously by the human body.[1] Instead, vitamins are synthesised by bacteria, yeasts, and plants.[2] As a result, adequate amounts of vitamins need to be supplied through the diet.[3] In total, an individual requires thirteen vitamins: four fat-soluble vitamins (A, D, E, K) and nine water-soluble vitamins, which comprise vitamin C (ascorbic acid) and eight B vitamins: thiamine (B1), riboflavin (B2), niacin (B3), pantothenic acid (B5), pyridoxine (B6), biotin (B7), folate/folic acid (B9) and cobalamin (B12).[1,3] Together, these B vitamins are collectively referred to as the B-group or 'vitamin B complex'.[4] This review provides a broad overview of the vitamin B complex, particularly its deficiencies, indications for supplementation, formulations, over-the-counter and scheduled preparations and potential drug-vitamin interactions.

The diversity of the vitamin B complex

Common features

The vitamin B complex is a group of water-soluble vitamins, which, given their solubility, are typically absorbed via carrier-facilitated transporters from the gastrointestinal tract, and undergo renal excretion.[5,6] Given its hydrophilicity and general low storage capacity, toxicity is typically low.[5,6]

Loss of the vitamin B complex from food products generally occurs due to processing, such as milling and refinement of plant sources (where vitamins are typically lost due to separation of the bran and germ), heating (particularly for thermolabile vitamins), or loss through leaching into water (e.g., through washing grains or distribution into cooking fluids which are often discarded).[5,6] Cooking fluids, such as gravy or soup made from animal products, help retain such vitamins that are lost.[5] South African regulations mandate the fortification of certain food products (e.g., wheat flour, maize meal) with several vitamins, including thiamine (as mononitrate), riboflavin, nicotinamide or niacinamide, pyridoxine (as hydrochloride), and folic acid, due to their importance and the losses often seen during processing.

Vitamin B sources

Vitamins are crucial for optimal physiological functions, and thus, the diet needs to be maintained appropriately to facilitate sufficient vitamin B complex levels (Table I), given the intricate convergent and divergent pathways that support healthy physiological functioning.[7]

Functions

The vitamin B complex serves as an essential cofactor in various enzymatic processes[12] that support cellular and physiological functioning.[9] Depending on the vitamin, supportive functions are diverse: major functions within the brain and nervous system,[12] the metabolism of carbohydrates, amino acids, fatty acids, and lipids, the synthesis of proteins, cholesterol, neurotransmitters, S-adenosyl methionine, and nucleotide bases,[13] immunological functions,[14] and mitigating or preventing various diseases, such as cardiovascular disease, neurodegenerative disorders, and neural tube defects.[12] Broad functions for each vitamin are provided in Table II.

Table I: Vitamin B types, dietary sources and recommended dietary allowance (RDA) values of vitamin B complex for males, non-pregnant females and pregnant females[8,9]

Type of vitamin B	Dietary sources	Recommended dietary allowance* (RDA)		
		Male	Non-pregnant female	Pregnant female
Thiamine (B1)	Whole grains, nuts,[6] pork, chicken, eggs, cereal sprouts, rice, bran and beans[2]	1.2 mg	1.1 mg	1.4 mg
Riboflavin (B2)	Leafy green vegetables, liver, eggs,[2] milk and dairy products, mushrooms and legumes[1]	1.3 mg	1.1 mg	1.4 mg
Niacin (B3)	Fish, meat, beans[2,6] and whole grains[10]	16 mg	14 mg	18 mg
Pantothenic acid (B5)	Nuts, mushrooms, whole grains, legumes, potatoes, tomatoes, yeast, meat, liver, eggs and milk[6]	5 mg	5 mg	6 mg
Pyridoxine (B6)	Whole grains, bananas, nuts, pork, poultry, fish, beef and organs[5]	1-1.7 mg	1-1.7 mg	1.9 mg
Biotin (B7)	Egg yolk, milk and dairy products, nuts, legumes, meat, certain vegetables and fruits[5]	30 µg	30 µg	30 µg
Folate/folic acid (B9)	Leafy green vegetables, legumes, citrus fruits, fortified cereals, avocado and liver[10]	400 µg	400 µg	600 µg
Cobalamin (B12)	Meat, liver, fish, shellfish and dairy products[11]	2.4 µg	2.4 µg	2.6 µg

*RDA values are referred to the daily required amounts adapted from the Institute of Medicine (US) Standing Committee on the Scientific Evaluation of Dietary Reference Intakes

Vitamin B deficiencies

Vitamin B deficiency may occur due to a variety of reasons, including malnutrition, malabsorption, alcoholism, genetic conditions, diseases, drug-nutrient interactions, and food processing.[5,6,21,22] For instance, diseases such as Crohn's disease, celiac disease, human immunodeficiency virus (HIV), and alcohol-use disorder may interfere with the body's ability to absorb B vitamins effectively.[23] Overall vitamin B deficiency leads to anaemia, digestive issues, skin conditions, infections, peripheral neuropathy, and psychiatric disorders,[24] however, depending on their functions and frequency of loss, unique symptoms may occur.

Given potential deficiencies, individuals may consider vitamin B supplements to mitigate these effects, either as over-the-counter or scheduled preparations (Table III). For instance, thiamine, riboflavin, pyridoxine and cobalamin are mainly involved in energy metabolism and are commonly used as dietary supplements.[21] A 2023 randomised double-blind trial found that supplementation with these B vitamins for 28 consecutive days significantly ($p < 0.05$) improved exercise endurance and reduced exercise fatigue in healthy, non-athletic adults at appropriate doses.[7] Another randomised controlled trial showed that 12 weeks of supplementation with oral thiamine, pyridoxine and cobalamin significantly decreased homocysteine levels in paediatric patients compared with baseline and placebo ($p < 0.001$)[25] as a result of homocysteine accumulation with cobalamin deficiency due to poor metabolism.[10] Furthermore, there was improved glycaemic control and renal function through lower homocysteine levels and could be a safe and effective strategy for treatment of early stage nephropathy in paediatric type 1 diabetes mellitus.[25] As such, a clear evidence-based approach can be applied in many vitamin B deficiencies.

Vitamin B-related pharmacotherapy

Examples of vitamin B supplementation is provided in Table III, with unique functions highlighted in Table II, which highlights its use not only for direct vitamin supplementation, but also to support the function of pharmacotherapy or mitigate adverse drug reactions. This includes iron and folic acid supplementation during pregnancy to improve maternal and neonatal outcomes including a reduction in low birth weight and preterm birth.[26] Additionally, the use of vitamins in tuberculosis (TB) patients are encouraged.[27] The World Health Organization (WHO) recommends pyridoxine when receiving high-dose isoniazid to patients with diabetes, uraemia, HIV infection, seizure disorders, alcohol abuse, malnutrition or peripheral neuropathy.[27]

Thiamine (B1)

Thiamine can be found in several dietary sources as its primarily phosphorylated form, including a range of plant- and animal-based foods.[2,6] Absorption is via carrier-mediated active transport, however, passive diffusion may occur at higher concentrations.[6] Anti-thiamine factors, which reduce the absorption of thiamine, are present as thermolabile and thermostable compounds in various food products, such as fermented fish, shellfish, and methylxanthine-containing teas and coffees.[6] Thermolabile factors can be deactivated by heating, but use of protective factors (such as ascorbic acid) or increasing the frequency between eating thiamine and anti-thiamine factors.[6]

Thiamine deficiency in the human diet leads to disturbances in numerous biochemical and metabolic processes, including impaired glucose metabolism, disrupted bioenergetic processes, mitochondrial dysfunction, lactic acidosis which is a consequence of pyruvate dehydrogenase (PDH) dysfunction in mitochondria.[28] Furthermore, it results in insufficient DNA synthesis due to reduced transketolase activity and ribose-5-phosphate synthesis in the pentose phosphate pathway as well as impaired neurotransmitter synthesis.[28]Although thiamine deficiency is rare in developed countries, it can occur as a result of poor dietary choices, certain medical conditions or intake of anti-thiamine elements.[10] Deficiency causes lethargy and, if left untreated, manifests in

Table II: Functions, regulatory health claims and dosage recommendations for vitamin B complex[15]

Vitamin B	Functions	Health supplement claim[a]		Recommended dose (Children)		Recommended dose (Adults)	
		Single substance products[b]	Multiple substance products[c]	Minimum	Maximum	Minimum	Maximum
Thiamine (B1) **To be calculated as thiamine*** i. Thiamine hydrochloride ii. Thiamine monochloride iii. Thiamine mononitrate iv. Thiamine monophos-phate v. Thiamine diphosphate vi. Thiamine pyrophos-phate	• Cofactor in carbohy-drate metabolism[6] • Amino and fatty acid hydrolysis[10] • Nervous system function (lipid, myelin, neurotransmitter and nucleic acid precursor synthesis)[6]	• Carbohydrate, protein and lipid metabolism • Energy production and metabolic processes • Nervous system and psychological function • Cardiac function • Growth and development • Maintenance of good health	• Carbohydrate, protein and lipid metabolism • Growth and development • Maintenance of good health • Multi-vitamin supplement/ Multi-vitamin/ mineral supplement	**1 to 13 years** 0.04 mg	≤ 100 mg	0.07 mg	≤ 100 mg
				14 to 18 years 0.07 mg	≤ 100 mg		
Riboflavin (B2) **To be calculated as riboflavin*** i. Riboflavin 5'-phosphate, sodium	• Enzymatic cofactor (flavin adenine mononucleotide [FMN], or flavin adenine dinucleotide [FAD])[6] • Carbohy-drate, protein and fat metabo-lism[10] • Niacin, folic acid, pyridoxine, and haem protein synthesis[9] • Maintenance of healthy skin, eyes, and nerve functions[10]	• Carbohydrate, protein and lipid metabolism • Energy production and metabolic processes • Nervous system functioning • Mucous membranes maintenance • Skin maintenance • Vision maintenance • Iron metabolism • Cell protection from oxidative stress • Tiredness and fatigue reduction • Tissue formation • Maintenance of good health	• Carbohydrate, protein and lipid metabolism • Tissue formation • Maintenance of good health • Multi-vitamin supplement/ Multi-vitamin/mineral supplement	**1 to 13 years** 0.04 mg	≤ 100 mg	0.08 mg	≤ 100 mg
				14 to 18 years 0.08 g	≤ 100 mg		
Nicotinic acid, Niacin and derivatives (B3) **To be calculated as niacin*,[d]** i. Nicotinic acid ii. Nicotinamide/ niacinamide iii. Nicotinamide ascorbate/ niacinamide ascorbate iv. Inositol hexanicoti-nate (inositol hexania-cinate)	• Co-factor, substrate and ligand[6] • Essential redox cofactors for cellular metabolism and antioxidant processes[6] • Supports glycolysis, Krebs cycle, fatty acid oxidation and synthesis[6] • Cholesterol and steroid production[6] • Alcohol metabolism[6] • Protection against oxidative stress and regulation of key biological processes including nutrient sensing, circadian rhythm, DNA repair, immune function, aging, and epigenetic control[6]	• Carbohydrate, protein and lipid metabolism • Mucous membranes maintenance • Skin maintenance • Psychological function • Tiredness and fatigue reduction • Growth and development • Maintenance of good health	• Carbohydrate, protein and lipid metabolism • Growth and development • Maintenance of good health • Multi-vitamin supplement/ Multi-vitamin/mineral supplement	**1 to 3 years** 0.6 mg	10 mg	1 mg	≤ 35 mg
				4 to 8 years 0.6 mg	15 mg		
				9 to 13 years 0.6 mg	20 mg		
				14 to 18 years 1 mg	30 mg		
Nicotinamide, niacinamide (B3)		• Carbohydrate, protein and lipid metabolism • Growth and development • Maintenance of good health	• Carbohydrate, protein and lipid metabolism • Growth and development • Maintenance of good health • Multi-vitamin supplement/ Multi-vitamin/mineral supplement	**1 to 3 years** 0.6 mg	10 mg	2.4 mg	≤ 500 mg
				4 to 8 years 0.6 mg	15 mg		
				9 to 13 years 0.6 mg	20 mg		
				14 to 18 years 1 mg	30 mg		

Table II: Functions, regulatory health claims and dosage recommendations for vitamin B complex[15]

Vitamin B	Functions	Health supplement claim[a]		Recommended dose (Children)		Recommended dose (Adults)	
		Single substance products[b]	Multiple substance products[c]	Minimum	Maximum	Minimum	Maximum
Pantothenic acid (B5) **To be calculated as d-pantothenic acid*,[e]** i. Calcium-d-pantothenate ii. Calcium-dl-pantothenate iii. Pantethine iv. d-Panthenol/Dexpanthenol v. dl-Panthenol vi. d-Pantothenic acid vii. dl-Pantothenic acid	• Coenzyme A and acyl-carrier protein (ACP) formation[6] • Catabolic and anabolic reactions (fatty acids, acetylcholine, and bile acid)[6] • Synthesis of fatty and amino acids[10] • Carbohydrate metabolism[10] • Fatty acid biosynthesis[10] • Biosynthesis of haemoglobin and cytochromes as a precursor of porphy-rin[16] • Gene expression[6] • Energy production and overall cellular function[10] • Maintains neurological functions, skin and mucosal health and cholesterol handling[6]	• Carbohydrate, protein and lipid metabolism • Energy production and metabolic processes • Steroid hormone, vitamin D and neurotransmitter synthesis and metabolism • Tiredness and fatigue reduction • Mental health performance • Tissue formation • Maintenance of good health	• Carbohydrate, protein and lipid metabolism • Tissue formation • Maintenance of good health • Multi-vitamin supplement/ Multi-vitamin/mineral supplement	**1 to 13 years** 0.2 mg	≤ 200 mg	0.4 mg	≤ 200 mg
				14 to 18 years 0.4 mg	≤ 200 mg		
Pyridoxine (B6) **To be calculated as pyridoxine*** i. Pyridoxal ii. Pyridoxal hydrochloride iii. Pyridoxal-5-phosphate (calcium salt) iv. Pyridoxamine v. Pyridoxamine-5-phosphate vi. Pyridoxine vii. Pyridoxine hydrochloride viii. Pyridoxine-5-phosphate	• Enzymatic cofactor[10] • Amino acid, lipid and carbohydrate metabolism[5] • Neurotransmitter synthesis[5] • Production of niacin from tryptophan[5] • Antioxidant processes[5] • Gene expression[5] • Immune and cardiovascular system health[5]	• Carbohy-drate, protein and lipid metabolism • Cysteine synthesis • Energy production and metabolic processes • Nervous system and psychological function • Homocysteine metabolism • Protein and glycogen metabolism • Red blood cell formation • Immune system function • Tissue formation • Tiredness and fatigue reduction • Hormonal activity regulation • Maintenance of good health	• Carbohydrate, protein and lipid metabolism • Tissue formation • Maintenance of good health • Multi-vitamin supplement/ Multi-vitamin/mineral supplement	**1 to 3 years** 0.05 mg	30 mg	0.1 mg	≤ 100 mg
				4 to 8 years 0.05 mg	40 mg		
				9 to 13 years 0.05 mg	60 mg		
				14 to 18 years 0.1 mg	80 mg		
Biotin (B7) **To be calculated as biotin*** i. D-biotin ii. Biocytin	• Co-enzyme in the activation of carboxylases to support fatty acid oxidation[5] • Gene expression alterations via biotinylation[5] • Promote immune function[5] • Used in beauty and wellness products for hair growth, nail strength, and improved skin[17]	• Carbohydrate, protein and lipid metabolism • Energy production and metabolic processes • Nervous system and psychological function • Normal hair maintenance • Mucous membranes maintenance • Skin maintenance • Maintenance of good health	• Carbohydrate, protein and lipid metabolism • Maintenance of good health • Multi-vitamin supplement/Multi-vitamin/mineral supplement	**1 to 13 years** 1 µg	≤ 500 µg	1.8 µg	≤ 500 µg
				14 to 18 years 1.8 µg	≤ 500 µg		

Table II: Functions, regulatory health claims and dosage recommendations for vitamin B complex[15]

Vitamin B	Functions	Health supplement claim[a]		Recommended dose (Children)		Recommended dose (Adults)	
		Single substance products[b]	Multiple substance products[c]	Minimum	Maximum	Minimum	Maximum
Folic acid/folate (B9) **To be calculated as folic acid*** i. Pteroylmonoglutamic acid ii. Calcium-L-methylfolate **Accepted source:** **5-Methyltetrahydrofolic acid**	• Synthesis of thymidine and purines for DNA construction and repair mechanisms[18] • Amino acid homeostasis[18] • Antioxidant mechanisms and epigenetic processes[18] • Promotes healthy erythrocytes and immune cells[19] • Mucosal and skin renewal, and cognitive functions[19] • Red blood cell formation[19] • Amino acid metabolism[19] • Supports embryogenesis and foetal development[18] • Prevents neural tube defects during pregnancy[20]	• Maternal tissue growth during pregnancy • Protein metabolism • Red blood cell formation • Reduces the risk of neural tube defects when taken daily prior to becoming pregnant and during early pregnancy • Maintenance of good health	• Protein metabolism • Red blood cell formation • Reduces the risk of neural tube defects when taken daily prior to becoming pregnant and during early pregnancy • Maintenance of good health • Multi-vitamin supplement/ Multi-vitamin/mineral supplement	**1 to 13 years** 15 µg	≤ 200 µg	30 µg	≤ 500 µg
				14 to 18 years 30 µg	≤ 500 µg		
Cyanocobalamin (B12) **To be calculated as cyanocobalamin*** i. Cyanocobalamin ii. Hydroxocobalamin iii. 5'-Deoxyadenosylcobalamin iv. Methylcobalamin	• Cofactor in DNA synthesis[10] • Red blood cell formation[10] • Nervous system function and maintenance [10] • Homocysteine metabolism[10] • Supports energy production [10] • Amino and fatty acid metabolism[10]	• Carbohydrate, protein and lipid metabolism • Cell division process • Red blood cell formation • Energy production and metabolic processes • Nervous system and psychological function • Homocysteine metabolism • Immune system function • Tiredness and fatigue reduction • Maintenance of good health	• Carbohydrate, protein and lipid metabolism • Red blood cell formation • Maintenance of good health • Multi-vitamin supplement/ Multi-vitamin/mineral supplement	**1 to 13 years** 0,09 µg	≤ 100 µg	0,14 µg	≤ 100 µg
				14 to 18 years 0.14 µg	≤ 100 µg		

*Various available forms of vitamin B that can be found in different sources; [a]Health supplement claim: A statement that indicates the intended beneficial effect of a product when used in accordance with its recommended conditions of use; [b]Single substance products: Fixed, pre-approved claims that apply strictly to products containing only one active ingredient, within its specified dosage range; [c]Multiple substance products: Broader, applicant-developed claims that apply to combination products where every ingredient's dosage and compatibility must collectively support the stated claim; [d]1 mg niacin equivalents = 1 mg niacin = 60 mg tryptophan; [e]1 mg d-pantothenic acid = 1.07 mg d-panthenol, 1 mg d-pantothenic acid = 0.92 mg calcium-d-pantothenate, 1 mg d-pantothenic acid = 0.5 mg dl-pantothenic acid, 1 mg d-pantothenic acid = 0.54 mg dl-panthenol, 1 mg d-pantothenic acid = 0.46 mg calcium-dl-pantothenate; f1 µg dietary folate equivalents (DFE) = 1 µg food folate, 1 µg DFE = 0.6 µg as supplement consumed with food, 1 µg DFE = 0.5 µg as supplement taken on an empty stomach

various pathologies, specifically beriberi which is cardiomyopathy with oedema and lactic acidosis, a condition that affects the peripheral nervous system and cardiovascular system,[2] and Wernicke-Korsakoff syndrome or Wernicke's encephalopathy.[28] Particularly in critically ill patients, renal excretion of thiamine may be increased, thus worsening clinical manifestations.[6] Supplementation with thiamine is generally recommended in cases of deficiency, malabsorption issues, or certain medical conditions[10] such as the management of Wernicke-Korsakoff syndrome and other disorders affecting thiamine absorption.[29]

Thiamine toxicity is low and rarely encountered unless at high doses, which in itself is often low risk considering oral supplementation above 5 mg has reduced uptake.[6] Adverse drug reactions may include heat sensitivity, allergic reactions (e.g., pruritic, urticaria, anaphylaxis), angioedema, cyanosis and excessive sweating.[6] Certain medication may induce pharmacokinetic interactions leading to reduced thiamine availability, such as diuretics (which increase urinary excretion), metformin (which reduces intestinal absorption) and 5-fluorouracil (which prevents activation).[6] Thiamine is included on the WHO's core list of essential medications for both adults and children indicating its importance as a prerequisite for a basic healthcare system.[30]

Riboflavin (B2)

Riboflavin is widely distributed in both plant- and animal-based foods.[1] Heating and washing of food products contribute to a loss of riboflavin, as well as exposure to light (350 to 560 nm), necessitating its storage in dark or shaded environments.[6] Absorption is in the small intestine via carrier-mediated transportation, while metabolism supports its conversion to active flavin mononucleotide or flavin adenine dinucleotide.[6]

Humans require dietary riboflavin for DNA repair, energy production, fatty acid and amino acid synthesis, folic acid activation, production of glutathione as free radical scavenger, and support of physiological systems, including the central nervous and renal system.[6,9] Riboflavin needs to be constantly supplied through the diet or supplementation due to it being poorly stored in the body.[31] Riboflavin deficiency rarely occurs alone, usually it is part of a generalised vitamin B deficiency because of diet or malabsorption.[31] It can occur as a result of lactation, phototherapy in infants, celiac sprue, malignancies, and alcoholism.[31] Riboflavin deficiencies may present as oedema and associated pain of the oral and mucous membranes, neurological deficiencies, hair loss, topical inflammation, cataract formation, and gastrointestinal malabsorption.[6] Additionally, riboflavin deficiency may also lead to ariboflavinosis, which presents with a sore throat, redness and swelling of the lining of the throat and corners of the lips, and inflammation and redness of the lining of the eyes.[10]

Riboflavin supplementation is recommended for treatment for deficiency, malabsorption issues, or certain medical conditions.[10] Riboflavin has shown beneficial use in deficiency-related diseases, including multiple acyl-coenzyme A dehydrogenase deficiencies, Brown-Vialetto-Von Laere syndrome and Fazio Londe disease.[6] Emerging research also explores its potential therapeutic applications in conditions such as migraine headaches[10] and potential preventable diseases management in anaemia, cancer, hyperglycaemia, hypertension, diabetes and oxidative stress.[32,33]

Toxicity induced by riboflavin is rare due to its saturable absorption from the gastrointestinal tract, and thus should it appear, it is generally confined to gastrointestinal adverse effects, such as nausea and vomiting.[6] Drug interactions are largely due to pharmacokinetic interactions with absorption or synthesis, for example, with doxorubicin (impaired flavin cofactor synthesis leading to riboflavin deficiencies) or phenothiazine-antipsychotics and tricyclic antidepressants (competitive inhibition due to structural similarities to flavin co-factors).[6]

Niacin (B3)

Niacin, generally in the form of nicotinic acid or nicotinamide, is obtained from animal-based foods which contain vitamin B3 as nicotinamide, and plant-based foods[10] which contain vitamin B3 as nicotinic acid.[2,6] However, humans can convert tryptophan to nicotinamide via the liver, although following a less preferential use pathway. Loss of niacin generally occurs via washing or milling, while heat does not significantly affect it.[6] Niacin is typically absorbed as nicotinamide intestinally via sodium-dependent facilitated diffusion, however, larger doses may occur via passive diffusion.[6] Metabolic conversion supports the formation of the active form, nicotinamide adenine dinucleotide.[6]

Common underlying reasons for niacin deficiency occurs due to poor diet, alcoholism, malabsorption or medications.[6] Severe niacin deficiency results in a condition known as pellagra,[10] which is a potential life-threating disease due to nutritional deficiencies, characterised by dermatitis, dementia, diarrhoea[6] and death if left untreated.[10] Additionally, milder forms of niacin deficiency may present as ulcerative colitis, acute cutaneous lupus erythematosus, Crohn disease, discoid lupus erythematosus, drug eruptions, drug-induced lupus erythematosus, drug-induced photosensitivity, drug-induced pemphigus and porphyria cutanea tarda.[34]

Niacin toxicity typically presents as flushing, burning and itching due to cutaneous vasodilation, which is generally the main contributor of cessation of treatment.[35] Otherwise, hypotension, headaches, gastrointestinal upsets (such as heartburn, ulceration, nausea and vomiting), and lactic acidosis may occur.[6]

Pantothenic acid (B5)

Pantothenic acid is ubiquitous and found in high levels in both plant- and animal-based products.[6] Pantothenic acid requires hydrolytic metabolism prior to intestinal absorption via sodium-dependent transporters or passive diffusion.[6] Loss of pantothenic acid generally occurs due to milling or leaching into cooking fluids, though heating does not typically contribute much to reduced levels.[6]

Deficiencies are rare given the ubiquitous nature of pantothenic acid, however, may occur due to malabsorption or malnutrition.[6]

Deficiency may appear as central nervous system (e.g., headaches, restlessness, fatigue, cramps) and digestive (diarrhoea, abdominal cramps) alterations, or insulin insensitivity.[6] Pantothenic acid supplementation is typically not required for individuals following a balanced diet, as it is easily available from various food sources.[10] However, supplementation may be considered in certain medical conditions or specific dietary restrictions, under the guidance of a healthcare professional.[10] In such cases, supplementation is administered as calcium pantothenate given its stability and solid form, as opposed to the viscous naturally occurring form of pantothenic acid.[6]

Toxicity is low and unlikely to occur within physiologically-relevant doses and use, though may precipitate diarrhoea at high levels.[6]

Pyridoxine (B6)

Pyridoxine comprises six related vitamers: pyridoxine, pyridoxal, pyridoxamine and 5′-phosphate esters (pyridoxine 5′-phosphate, pyridoxal 5′-phosphate, pyridoxamine 5′-phosphate) thereof.[5] Metabolic conversion produces the active form, pyridoxal 5′-phosphate, which serves as a co-factor.[5] Various plant and animal sources provide pyridoxine.[5] Heating of food typically causes a decrease in the available content,[5] as well as milling. Intestinal absorption of pyridoxine is facilitated by transporters.[5] Several anti-pyridoxine factors are also found in food, such as gingko, flaxseed and a variety of herbal remedies.[5] Such factors interfere with pyridoxine absorption thus precipitating potential deficiencies.[5]

Deficiencies are typically through dietary limitations and malabsorption, alcoholism, or through drug interactions or genetic variation.[5] Drug interactions which can precipitate deficiencies include caffeine and theophylline (which reduced bioactivation of pyridoxine), hydrazine, levodopa, and isoniazid (which inactivates pyridoxal 5′-phosphate),[5] or phenytoin, carbamazepine and valproate (which increase vitamer metabolism).[5] Characteristic outcomes include a variety of health disorders due to limited metabolic processing, such as poor neurotransmitter synthesis, seborrheic dermatitis, cheilosis, anaemia, neuropathy, mental health disorders, seizures (such as due to pyridoxine-dependent epilepsy), cardiovascular concerns, and immune dysfunction.[5] In cases of overdoses with anti-riboflavin factors (including certain medication, like isoniazid), pyridoxine supplementation can serve as antidote, or be given prophylactically to mitigate adverse drug reactions (such as isoniazid-induced peripheral neuropathy).[5] Pyridoxine supplementation are only necessary in certain medical conditions, such as certain types of anaemia or neurological disorders, however under the guidance of a healthcare professional.[10]

Chronic high dose supplementation may paradoxically precipitate neurodegeneration reversible peripheral neuropathy, similar to what is seen with deficiency, likely due to competition between the inactive and active form.[5]

Biotin (B7)

Biotin is present in various plant- and animal-based foods.[5,36] Biotin is commonly found either as free biotin or as protein-bound biocytin, where the latter's biotin is released by biotindase.[5] Avidin, a naturally occurring anti-biotin molecule (present in egg white), binds biotin to deactivate it and prevent its absorption, however, cooking denatures avidin to allow for the release of biotin.[5] Biotin loss during food processing is primarily due to milling and leaching (although protein-bound biotin is less likely to be lost), but heating may also cause a slight decrease.[5] Intestinal absorption of free biotin occurs via sodium-dependent transporters.[5]

Biotin deficiency is rare, due to the various available biotin-containing food sources, however may develop in certain populations who are at a higher risk.[37] This includes individuals on prolonged antibiotic treatment (disrupted intestinal microbiota), individuals receiving chronic anticonvulsant treatment (disrupted biotin metabolism), and individuals on complete parenteral nutrition with insufficient biotin supplementation.[37] Clinical presentation of biotin deficiency may include seizures, low muscle tone, uncoordinated movement, respiratory distress, rashes and decreased physical and cognitive growth.[5] Folate supplementation may be recommended to meet the increased nutritional demands in cases such as pregnancy, malabsorption issues and more severe cases.[10]

Given its extensive excretion, toxicity is low and biotin supplementation is considered safe[5] though potential neurological effects may occur.

Folate/folic acid (B9)

Vitamin B9, termed folate (naturally occurring) or folic acid (synthetic),[18] is mainly found in plant-based foods and animal-based foods.[10] Natural food sources which contain folate generally have a high bioavailability, therefore it is important to follow a well-balanced diet for maintaining adequate folate levels.[38]

Insufficient folate consumption has been associated with several health problems, including an increased risk of neural tube defects in neonates, anaemia, and possible contribution to cardiovascular diseases.[10] Folate deficiency may often be due to nutritional malabsorption or malnutrition, alcoholism or several diseases (such as atrophic gastritis).[22] Folic acid deficiency may precipitate neural tube defects during embryogenesis or megaloblastic anaemia.[18] Therefore in certain cases, such as pregnancy or individuals with malabsorption issues, folate supplementation may be recommended to meet the increased nutritional requirements.[10]

Cobalamin (B12)

Cobalamin and its analogues are collectively called cobamides (also known as corrinoid cofactors) which are found in certain food products and produced by microorganisms in the human gut.[39] However, humans are generally unable to make use of the various cobamides other than cobalamin.[39] This is due to the

Table III: Commonly used vitamin B medications in South Africa,[41] including medication where vitamin B is included for adverse drug reaction mitigation

Examples (schedule)	Active ingredient	Formulation	Dose	Administration	Indications
Vitamin supplementation-dominant indications					
A-Lennon Vitamin B Complex Injection (S3)	Nicotinamide, thiamine hydrochloride, d-panthenol, pyridoxine hydrochloride and riboflavin	Injection	Per 1 mL Nicotinamide 100 mg Thiamine hydrochloride 10 mg d-Panthenol 5 mg Pyridoxine hydrochloride 5 mg Riboflavin 2 mg	Deficiency reversible with oral thiamine doses 500 µg daily Therapeutic dose: 1-2 ml daily 2 ml injection: Intramuscular or slow intravenous injection (with caution) 10 ml injection: Slow intramuscular injection only[42]	Vitamin deficiencies
A-Lennon Vitamin B12 Injection (S3)	Cyanocobalamin	Injection	1.000 µg/mL	Intramuscular administration No neurological involvement: 250-1000 µg on alternate days (1–2 weeks), then 250 µg weekly; maintenance 1000 µg monthly Neurological involvement: 1000 µg on alternate days until clinical improvement Prophylaxis: 250-1000 µg monthly[42]	Vitamin B12 deficiencies related to megaloblastic anaemia, neurological conditions, pernicious anaemia, nutrient deficiency-linked macrocytic anaemia, intestinal malabsorption, diet-related deficiencies, and post-gastrectomy
Beespan (S1)	Combination of vitamin B1, 2, 6, and 12, and calcium pantothenate	Capsules	Vitamin B1 100 mg Vitamin B2 20 mg Vitamin.B6 200 mg Vitamin B12 200 µg Calcium pantothenate 20 mg	1 capsule daily	Vitamin B complex deficiencies, such as peripheral neuritis prophylaxis in isoniazid/ hydralazine treatment
Be-Tabs Folic Acid (S1)	Folic acid	Tablets	Folic acid 5 mg	Megaloblastic anaemia: Initial 10 to 20 mg daily for 14 days, with 2.5 to 10 mg daily maintenance thereafter Megaloblastic anaemia of pregnancy prophylaxis: 200 to 500 µg daily	Megaloblastic anaemia treatment and prophylaxis
Chocaton (S0)	Combination of vitamins A, B1, B2, B6, B12, C, D3 and E, and calcium pantothenate and nicotinamide	Syrup	Per 10 ml Vitamin A 5.000 iu Vitamin B1 2 mg Vitamin B2 2 mg Vitamin B6 2.5 mg Vitamin B12 1 µg Calcium pantothenate 1 mg Nicotinamide 5 mg Vitamin C 50 mg Vitamin D3 400 iu Vitamin E 1.65 mg	Adults: 5 to 10 mL daily Children < 6 years: 2.5 mL daily	Vitamin deficiencies
Neurobion (S1)	Combination of vitamins B1, B6 and B12	Tablets	Vitamin B1 100 mg Vitamin B6 200 mg Vitamin B12 200 µg	1 tablet daily	Vitamin deficiencies
Neurobion (S3)	Combination of vitamins B1, B6 and B12	Injection (ampoules)	Per 3 mL Vitamin B1 100 mg Vitamin B6 100 mg Vitamin B12 1000 µg	Deep intramuscular injection Severe cases: 1 ampoule daily until acute symptoms subside Mild cases and follow-up therapy: two to three ampoules per week	Vitamin deficiencies
Soluvit Novum (S3)	Combination of vitamins B1, B2, B6, B12,and C, and nicotinamide, pantothenic acid, biotin, and folic acid	Lyophilised powder for solution for infusion	Vitamin B1 3.2 mg Vitamin B2 3.6 mg Vitamin B6 4 mg Vitamin B12 5 µg Vitamin C 100 mg Nicotinamide 40 mg Pantothenic acid 15 mg Biotin 60 µg Folic acid 0.4 mg	Reconstituted mixture added to intralipid/glucose solutions for infusion Adults and children over 10 kg: 1 vial in 10 mL water for injection Children < 10 kg: 1/10 of contents of one vial per kg body mass	Adults and paediatric nutrient supplementation

Table III: Commonly used vitamin B medications in South Africa,[41] including medication where vitamin B is included for adverse drug reaction mitigation

Examples (schedule)	Active ingredient	Formulation	Dose	Administration	Indications
Vitamin supplementation included to support other active ingredients for uptake, action or adverse drug reaction mitigation					
Asic (S2)	Dicyclomine hydrochloride, doxylamine succinate and pyridoxine hydrochloride	Tablets	Dicyclomine hydrochloride 10 mg Doxylamine succinate 10 mg Pyridoxine hydrochloride 50 mg	2 tablets at bedtime Severe cases: 1 tablet before rising and 1 tablet mid-afternoon	Pregnancy-related nausea and vomiting
Autrin (S1)	Iron fumarate, ascorbic acid, intrinsic factor concentrate, folic acid and vitamin B12	Capsules	Iron fumarate 349.755 mg Ascorbic acid 150 mg Intrinsic factor concentrate 75 mg Folic acid 2 mg Vitamin B12 15 µg	1 capsule daily with or after meals	Common anaemia treatment and maintenance
Cotrizid (S4)	Isoniazid, pyridoxine hydrochloride, sulfamethoxazole and trimethoprim	Tablets	Isoniazid 300 mg Pyridoxine hydrochloride 25 mg Sulfamethoxazole 800 mg Trimethoprim 160 mg	Best taken after meals. Adults and children ≥ 25 kg: 1 tablet once daily. Children 14 to < 24.9 kg: half a tablet once daily	Pyridoxine supplementation to mitigate isoniazid-induced peripheral neuropathy
Ferrimed (S1)	Iron(III)-hydroxide polymaltose complex and folic acid	Capsules	Iron(III)-hydroxide polymaltose complex equivalent to 50 mg elemental iron Folic acid 150 µg	Take in divided doses with meals Therapeutic dose: 2 to 4 capsules/day Supplement dose: 1 to 2 capsules daily	Folic acid supplementation to support erythrocyte maturity
Yasmin Plus (S4)	Drospirenone, ethinylestradiol and levomefolate calcium	Tablets	Hormone-containing tablets Drospirenone 3 mg Ethinylestradiol 0.03 mg Levomefolate calcium 0.451 mg Hormone-free tablets Levomefolate calcium 0.451 mg	1 tablet at the same time daily for 28 days Commenced from the first day of the menstrual cycle	Levomefolate to support foetus development
Yaz Plus (S4)	Drospirenone, ethinylestradiol and levomefolate calcium	Tablets	Hormone-containing tablets Drospirenone 3 mg Ethinylestradiol 0.02 mg Levomefolate calcium 0.451 mg Hormone-free tablets Levomefolate calcium 0.451 mg	1 tablet at the same time daily for 28 days Commenced on the first day of the menstrual cycle	Levomefolate to support foetus development

selectivity of the cobalamin uptake and the trafficking system.[39] In the intestine a glycoprotein known as intrinsic factor (IF), binds to cobalamin with very high (femtomolar) affinity and facilitates its absorption into ileal cells.[39] This process includes both naturally occurring forms, such as adenosyl cobalamin, and synthetic forms, such as cyanocobalamin.[39] Cobalamin is solely obtained from the diet or supplementation, with most sources including animal-based products.[11] Cobalamin is also fortified in few plant-based foods.[10] Intestinal uptake is mediated through carrier proteins such as haptocorrin, intrinsic factor, and transcobalamin.

While cobalamin is primarily found in animal products, its absence in plant-based sources poses as a challenge for individuals following vegetarian or vegan diets[10] who remain at a higher risk of cobalamin deficiency given its lack in higher order plants.[40]

Deficiencies of cobalamin are characterised by megaloblastic anaemia, decreased cardiovascular function and neurological issues. Conditions such as pernicious anaemia, Crohn's disease, celiac disease, and gastrointestinal surgery can interfere with the absorption of cobalamin leading to deficiency.[10] Impaired intrinsic factor availability (due to parietal cell destruction immune cells) precipitates pernicious anaemia.[21,40] Neurological issues including peripheral neuropathy (tingling, numbness, and pain in the hands and feet), difficulty walking, balance problems, memory loss, confusion, and severe neurological damage in advanced cases.[10] Cobalamin deficiency may occur due to alcoholism, decreased intestinal absorption due to disease, medication use (such as proton pump inhibitors), or nutrient constraints in the diet.[21,22] As a result of the elevated levels of homocysteine due to cobalamin deficiency, there is an increase in the risk of cardiovascular disease, including heart attack and stroke.[10]

Drug-vitamin interactions

Like various other dietary supplements, vitamin B supplements may interact with clinically relevant drugs, known as a drug-vitamin interaction.[43] Dietary supplements contain active chemical constituents that can interact with drugs at physical, chemical,

Table IV: Potential drug-vitamin interactions[43]

Vitamin	Drug	Drug-Vitamin Interaction	Clinical implication
Thiamine (B1)	Furosemide	Increased thiamine urinary excretion	Thiamine deficiency
	Phenytoin (long-term use)	Decreased thiamine blood levels	
	Digoxin	Decreased thiamine absorption by cardiomyocytes (especially when combined with furosemide)	
Riboflavin (B2)	Phenobarbital (long-term use)	Increased riboflavin destruction	Riboflavin deficiency
	Hydrochlorothiazide and probenecid	Increased riboflavin urinary excretion and decreased absorption	
	Oral contraceptive pills	Decreased riboflavin nutritional status	
	Antipsychotics (phenothiazine, chlorpromazine), tricyclic antidepressants, tetracycline, antimalarials (quinacrine), anticancer (adriamycin, doxorubicin)	Inhibited incorporation of riboflavin into FAD and FMN	
	Anticholinergics, tetracycline, tricyclic antidepressants (imipramine, desipramine, amitriptyline), antiepileptics (phenytoin), antipsychotics (chlorpromazine), doxorubicin, methotrexate	Decreased riboflavin absorption	
Niacin (B3)	Statins	Additive impairment of skeletal muscle functioning	Rhabdomyolysis
	Sulfinpyrazone	Decreased uric acid excretion	Inhibited uricosuric effect
	Antihypertensives	Increased efficacy of antihypertensives	Hypotension
	Oral hypoglycaemics (metformin, glipizide, glyburide) and insulin	Decreased efficacy of oral hypoglycaemics	Hyperglycaemia
	Nicotine patches	Additive vasodilation of cutaneous blood vessels	Increased skin flushing
	Anticoagulants (warfarin)	Elevated International Normalised Ratio (INR) due to synergistic coagulopathy	Increased bleeding
	Carbamazepine, primidone	Increased niacin efficacy	Niacin toxicity
	Isoniazid, tetracycline, azathioprine, chloramphenicol, cycloserine, fluorouracil, levodopa and carbidopa, phenytoin, valproic acid, mercaptopurine, colestipol, welchol, cholestyramine	Decreased niacin efficacy	Niacin deficiency
Pantothenic acid (B5)	Oral contraceptive pills	Decreased pantothenic acid efficacy	Pantothenic acid deficiency
Pyridoxine (B6)	Antiepileptics (phenytoin, phenobarbital)	Decreased epileptic efficacy	Suboptimal control of seizures
	Levodopa	Decreased levodopa efficacy	Suboptimal control of Parkinson's disease
	Isoniazid	Decreased pyridoxine efficacy	Peripheral neuropathy
	Cycloserine	Increased pyridoxine urinary excretion	Neurotoxicity
	Amiodarone		Photosensitivity and dermatitis
	Theophylline	Decreased bioavailability of pyridoxine	Pyridoxine deficiency
	Erythropoietin therapy	Decreased pyridoxine blood levels	
	Penicillamine	Decreased pyridoxine efficacy	
	Nonsteroidal anti-inflammatory drugs, monoamine oxidase inhibitors, oral contraceptive pills, hydralazine, theophylline, tetracycline	Decreased pyridoxine metabolism	Pyridoxine toxicity
Folate/folic acid (B9)	Methotrexate	Decreased anticancer activity	Chemotherapy treatment failure
	Phenytoin, carbamazepine, valproate	Decreased serum levels of antiepileptics	Seizures
	Pyrimethamine	Decreased antimalarial efficacy	Persistent infection
	Trimethoprim, triamterene, pyrimethamine, sulfasalazine	Exhibit antifolate activity	Folate deficiency
	Histamine H2 receptor antagonists, proton pump inhibitors, nonsteroidal anti-inflammatory drugs, phenytoin, phenobarbital, primidone, cholestyramine, cholestipol	Decreased folate metabolism	Folate toxicity
Cobalamin (B12)	Metformin, histamine H2 receptor antagonists, proton pump inhibitors	Decreased cobalamin absorption	Cobalamin deficiency
	Oral contraceptive pills	Decreased serum cobalamin concentrations	
	Phenytoin, phenobarbital, primidone, methotrexate, colchicine, bile acid sequestrants (cholestyramine, colesevelam), tetracycline	Decreased cobalamin metabolism	Cobalamin toxicity

physiological, and pathophysiological levels[43] which may lead to an adverse event such as those listed in Table IV. In many cases, such interactions impact the availability of the vitamin, leading to a deficiency, or may impact the treatment success of the medication.

Conclusion

The vitamin B complex is composed of eight water-soluble B vitamins which primarily functions as an enzymatic cofactor by supporting various physiological processes such as energy production, macronutrient (carbohydrate, protein and fat) metabolism and neurological system functions. Although there is an overlap of functions, each vitamin has unique characteristics regarding food sources, absorption and transport mechanisms, required values for optimal functioning, available supplementation and clinical outcomes when interacting with other medications. As shown in this review, vitamin B deficiencies present as serious symptoms and requires supplementation when necessary. South Africa has a range of vitamin B supplements to treat deficiencies, but an individual receiving supplementation should inform their healthcare professional of currently used concomitant medication to prevent drug-vitamin interactions. It is also important to take note of the RDA values when supplementing, to prevent vitamin B toxicity.

Conflict of interest

The authors declare no conflict of interest.

ORCID

M Naidoo https://orcid.org/0009-0003-2579-9744

W Cordier https://orcid.org/0000-0002-5744-9285

References

1. Kennedy DO. B vitamins and the brain: Mechanisms, dose and efficacy - a review. Nutrients. 2016;8(2):68. https://doi.org/10.3390/nu8020068.
2. Yoshii K, Hosomi K, Sawane K, Kunisawa J. Metabolism of dietary and microbial vitamin B family in the regulation of host immunity. Front Nutr. 2019;6:48. https://doi.org/10.3389/fnut.2019.00048.
3. Akram M, Munir N, Daniyal M, et al. Vitamins and minerals: Types, sources and their functions. Functional foods and nutraceuticals: bioactive components, formulations and innovations: Springer; 2020. p. 149-72. https://doi.org/10.1007/978-3-030-42319-3_9.
4. Schellack G, Harirari P, Schellack N. B-complex vitamin deficiency and supplementation. SA Pharm J. 2016;83(4):14-9.
5. Dias P, Siatka T, Vopršalová M, et al. Biological properties of vitamins of the B-complex, part 2: vitamins B6 and B7 (biotin, vitamin H). Nutr Res Rev. 2025;38(2):791-824. https://doi.org/10.1017/S0954422425100097.
6. Hrubša M, Siatka T, Nejmanová I, et al. Biological properties of vitamins of the B-complex, part 1: vitamins B1, B2, B3, and B5. Nutrients. 2022;14(3):484. https://doi.org/10.3390/nu14030484.
7. Lee M-C, Hsu Y-J, Shen S-Y, Ho C-S, Huang C-C. A functional evaluation of anti-fatigue and exercise performance improvement following vitamin B complex supplementation in healthy humans, a randomised double-blind trial. Int J Med Sci. 2023;20(10):1272-1281. https://doi.org/10.7150/ijms.86738.
8. Institute of Medicine (US) Standing Committee on the scientific evaluation of dietary reference intakes and its panel on folate, other B vitamins, and choline. dietary reference intakes for thiamine, riboflavin, niacin, vitamin B6, folate, vitamin B12, pantothenic acid, biotin, and choline. Washington (DC): National Academies Press (US); 1998. PMID: 23193625.
9. Hanna M, Jaqua E, Nguyen V, Clay J. Vitamins: Functions and uses in medicine. Perm. J. 2022;26(2):89-97. https://doi.org/10.7812/TPP/21.204.
10. Atasever M İM, Altun SK, Paksoy N, Harem İŞ. Article and reviews in health sciences. Güngör S AD, editor. Ankara, Turkey: Platanus Publishing; 2024.
11. O'Leary F, Samman S. Vitamin B12 in health and disease. Nutrients. 2010;2(3):299-316. https://doi.org/10.3390/nu2030299.
12. Saini S, Rathore A, Suresh N, Singh V. Vitamins A, B, C, D, E, and K as molecular modulators: Integrative roles in precision medicine, nutrigenomics, therapy, and disease prevention. Indian J Precis Med Mol Med. 2025;1(2):44-52. https://doi.org/10.4103/IJPMMM.IJPMMM_10_25.
13. Sechi G, Sechi E, Fois C, Kumar N. Advances in clinical determinants and neurological manifestations of B vitamin deficiency in adults. Nutr Rev. 2016;74(5):281-300. https://doi.org/10.1093/nutrit/nuv107.
14. Prasad S, Pandey VK, Singh K, et al. A comprehensive review on nutritional interventions and nutritive elements: Strengthening immunity for effective defense mechanism during pandemic. Food Sci Nutr. 2024;12(7):4534-45. https://doi.org/10.1002/fsn3.4138.
15. South African Health Products Regulatory Authority. Complementary medicines - Health supplements: Safety and efficacy. 2022;4(3).
16. Ball GF. Vitamins in foods: Analysis, bioavailability, and stability: CRC Press; 2005. https://doi.org/10.1201/9781420026979.
17. John JJ, Lipner SR. Consumer perception of biotin supplementation. J Cutan Med Surg. 2019;23(6):613-6. https://doi.org/10.1177/1203475419871046.
18. Premjit Y, Pandey S, Mitra J. Recent trends in folic acid (vitamin B9) encapsulation, controlled release, and mathematical modelling. Food Rev Int. 2023;39(8):5528-62. https://doi.org/10.1080/87559129.2022.2077361.
19. Subar A, Block G, James L. Folate intake and food sources in the US population. Am J Clin Nutr. 1989;50(3):508-16. https://doi.org/10.1093/ajcn/50.3.508.
20. Iyer R, Tomar S. Folate: A functional food constituent. J Food Sci. 2009;74(9):R114-22. https://doi.org/10.1111/j.1750-3841.2009.01359.x.
21. Green R, Allen LH, Bjørke-Monsen A-L, et al. Vitamin B12 deficiency. Nat Rev Dis Primers. 2017;3:17040. https://doi.org/10.1038/nrdp.2017.40. Erratum in: Nat Rev Dis Primers. 2017;3:17054. https://doi.org/10.1038/nrdp.2017.54.
22. Fenech M. The role of folic acid and Vitamin B12 in genomic stability of human cells. Mutat Res. 2001;475(1-2):57-67. https://doi.org/10.1016/S0027-5107(01)00079-3.
23. Sarwar MF, Sarwar MH. Deficiency of vitamin B-complex and its relation with body disorders [Internet]. B-complex vitamins: Sources, intakes and novel applications. IntechOpen; 2022. https://doi.org/10.5772/intechopen.99456.
24. Rathee S, Nayak V, Singh KR, Ojha A. Nanofortification of vitamin B-complex in food matrix: need, regulations, and prospects. Food Chem (Oxf). 2022;4:100100. https://doi.org/10.1016/j.fochms.2022.100100.
25. Elbarbary NS, Ismail EAR, Zaki MA, et al. Vitamin B complex supplementation as a homocysteine-lowering therapy for early stage diabetic nephropathy in pediatric patients with type 1 diabetes: A randomised controlled trial. Clin Nutr. 2020;39(1):49-56. https://doi.org/10.1016/j.clnu.2019.01.006.
26. Bekele Y, Gallagher C, Batra M, et al. Is oral iron and folate supplementation during pregnancy protective against low birth weight and preterm birth in Africa? A systematic review and meta-analysis. Nutrients. 2024;16(16):2801. https://doi.org/10.3390/nu16162801.
27. Patti G, Pellegrino C, Ricciardi A, et al. Potential role of vitamins A, B, C, D and E in TB treatment and prevention: A narrative review. Antibiotics (Basel). 2021;10(11):1354. https://doi.org/10.3390/antibiotics10111354.
28. Mrowicka M, Mrowicki J, Dragan G, Majsterek I. The importance of thiamine (vitamin B1) in humans. Biosci Rep. 2023;43(10):BSR20230374. https://doi.org/10.1042/BSR20230374.
29. Kerns JC, Arundel C, Chawla LS. Thiamin deficiency in people with obesity. Adv Nutr. 2015;6(2):147-53. https://doi.org/10.3945/an.114.007526.
30. World Health Organization [Internet]. Model List of Essential Medicines; 1977 [updated 2025 Sep; cited 2026 Apr 7]. Available from: https://list.essentialmeds.org/.
31. Buehler BA. Vitamin B2: Riboflavin. J Evid Based Complementary Altern Med. 2011;16(2):88-90. https://doi.org/10.1177/1533210110392943.
32. Pinto JT, Zempleni J. Riboflavin. Adv Nutr. 2016;7(5):973-5. https://doi.org/10.3945/an.116.012716.
33. Sina RE, Daley SF. Riboflavin Deficiency. 2026 Apr 13. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026 Jan. PMID: 29262062.
34. Redzic S, Hashmi MF, Gupta V. Niacin deficiency. [Updated 2023 Jul 25]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK557728/.
35. Javaid A, Mudavath SL. Niacin-induced flushing: Mechanism, pathophysiology, and future perspectives. Arch Biochem Biophys. 2024;761:110163. https://doi.org/10.1016/j.abb.2024.110163.
36. EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), Turck D, Bresson J-L, Burlingame B, et al. Scientific opinion on dietary reference values for riboflavin. EFSA J. 2017;15(8):4919. https://doi.org/10.2903/j.efsa.2017.4919.
37. Saleem F, Soos MP. Biotin deficiency. Cureus. 2019;9(12):e1984.
38. Chan Y-M, Bailey R, O'Connor DL. Folate. Adv Nutr. 2013;4(1):123-5. https://doi.org/10.3945/an.112.003392.
39. Sokolovskaya OM, Plessl T, Bailey H, et al. Naturally occurring cobalamin (B12) analogs can function as cofactors for human methylmalonyl-CoA mutase. Biochimie. 2021;183:35-43. https://doi.org/10.1016/j.biochi.2020.06.014.
40. Smith AD, Refsum H. Vitamin B-12 and cognition in the elderly. Am J Clin Nutr. 2009;89(2):707S-11S. https://doi.org/10.3945/ajcn.2008.26947D.
41. mobiMIMS [Internet]. mobiMIMS: Electronic. 2025 [cited 2026 Mar 21]. Available from: https://www.mobimims.co.za/.
42. SAHPRA. SAHPRA [Internet]. PI and PIL repository. [cited 2026 Apr 7]. Available from: https://pi-pil-repository.sahpra.org.za/.
43. Bachmann G, Bakris GL, Barone JA, et al. Iatrogenicity: Causes and consequences of iatrogenesis in cardiovascular medicine. Rutgers University Press; 2018.

Influenza vaccination: a practical update for pharmacists

M Sibanda,[1,2] **M Munzhedzi,**[1,2] **Z Ismail,**[1,2] **RJ Burnett,**[1,2] **JC Meyer**[1,2]

[1] Department of Public Health Pharmacy and Management, Sefako Makgatho Health Sciences University, South Africa

[2] South African Vaccination and Immunisation Centre, Sefako Makgatho Health Sciences University, South Africa

Corresponding author, email: mncengeli.sibanda@smu.ac.za

Abstract

Worldwide, seasonal influenza epidemics and sporadic influenza pandemics result in high morbidity and mortality rates. The immunocompromised, individuals with chronic health conditions, older adults, infants and pregnant women are most at risk of severe morbidity and mortality from influenza. Annual vaccination remains the most cost-effective strategy for preventing influenza and reducing influenza-related complications, hospitalisations and deaths. Despite clear public health benefits, vaccine uptake remains suboptimal due to limited awareness, misconceptions about vaccine safety and effectiveness, low perceived influenza risk, and logistical access barriers. Pharmacists are well-positioned to improve vaccine uptake through targeted interventions such as advocacy and patient education, and directly through vaccine administration, stock management, cold-chain management and adverse event following immunisation monitoring.

Keywords: influenza, vaccination, immunisation, prevention, health communication

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Introduction

Influenza remains a major global public health concern, with a high disease burden and significant economic impact. Approximately 3–5 million cases of severe influenza resulting in an estimated 290 000–650 000 respiratory deaths, occur annually.[1-3] Influenza (along with pneumonia) is one of the top 10 underlying natural causes of death in South Africa, ranked 6th for the period 2021–2023.[4] A modelling study based on 2013–2015 South African data, estimated that 10.7 million influenza-related illnesses and 11 536 deaths from influenza occurred annually.[5]

Influenza is a highly contagious acute respiratory illness caused by influenza viruses. Both influenza types A and B cause seasonal epidemics; however, influenza A is also responsible for most global influenza pandemics.[3,6] In South Africa, the influenza season typically occurs during the winter months. However, the National Institute for Communicable Diseases (NICD) reported that in 2025, the season started as early as March and ended in July, while out-of-season smaller increases were observed in September/October and again in November/December.[6] Similarly, the 2026 influenza season started in early March.[7] The influenza virus genome allows rapid evolution via gene exchange/reassortment (antigenic shift) and mutations (antigenic drift), which determine its virulence and circulation.[6,8]

Respiratory droplets released during coughing or sneezing is the primary mode of transmission, and infection typically occurs from close contact (within 1 to 2 meters) with an infected person or touching contaminated fomites.[6,9,10] The upper respiratory tract, which includes the nose, throat, bronchi, and occasionally the lungs, is the primary site of influenza infection, although it can also affect the heart, brain, and muscles.[6,8] The symptoms vary in severity and include fever, chills, headaches, myalgia, arthralgia, pharyngitis, coughing and rhinitis/coryza. Viral shedding commonly occurs from a few days before to a week after symptom onset, but may persist for >10 days in infants and adults with severe disease, and even longer in severely immunocompromised patients.[6,8]

Most people recover from influenza within a few days; however, it can cause complications resulting in hospitalisation and/or death, particularly among high-risk populations including pregnant women, infants, older adults (≥ 65 years) and individuals who have chronic health conditions or are immunocompromised.[6] In adults, influenza is the main viral cause of community-acquired pneumonia (CAP) and increases the risk of secondary bacterial infections, including pneumococcal pneumonia, the primary cause of bacterial CAP.[11] Influenza illness may result in absenteeism, or hospitalisation and/or death which has a significant negative impact on both the economy and the healthcare system.[12-14] With the rise of antimicrobial resistance (AMR), influenza vaccines are a critical, yet underutilised tool to mitigate AMR through preventing infections, reducing antibiotic use, and curbing the spread of resistant bacteria.[15]

Prevention of influenza

Primary prevention remains the cornerstone of reducing the spread and impact of influenza, particularly among vulnerable populations at increased risk of severe disease and complications.[6,10] Although vaccination is the most effective strategy for preventing influenza and its associated outcomes, a comprehensive primary prevention approach should also include non-pharmaceutical interventions.[6,16] These include regular hand hygiene, respiratory etiquette such as covering coughs and sneezes, appropriate use of face masks in high-risk settings, staying home when symptomatic, and ensuring adequate ventilation in indoor environments.[6]

Influenza vaccine composition and recommendations

Influenza vaccine effectiveness and safety

Vaccination against influenza is considered the most cost-effective infection control and prevention strategy, averting up to 59% of infections in healthy adults while causing mostly minor adverse events following immunisation (AEFI).[10,17] Serious AEFI with the influenza vaccine are rare and include severe allergic reactions which usually occur shortly after immunisation. Typical AEFI include short-lived self-limiting systemic side-effects such as transient fever, body aches, headaches and fatigue, and local reactions such as pain and swelling at the injection site.[10,17]

Types and composition of influenza vaccines

The vaccines available in South Africa are egg-based; either a split-virion or a sub-unit inactivated influenza vaccine (IIV). These vaccines are updated annually with the strain composition recommendations of the World Health Organization (WHO) for the southern hemisphere, which are based on global influenza surveillance data, antigenic analysis and expert review to maximise vaccine effectiveness.[18] Based on the WHO recommendations for the 2026 influenza season, the influenza vaccine should contain three strains, referred to as a trivalent vaccine.[18]

Egg-based vaccines should contain the following strains:

- A/Missouri/11/2025(H1N1)pdm09-like virus
- A/Singapore/GP20238/2024(H3N2)-like virus
- B/Austria/1359417/2021(B/Victoria lineage)-like virus.[18]

In the past, quadrivalent influenza vaccines protected against an additional B/Yamagata lineage virus. However, based on the absence of confirmed detection of naturally occurring B/Yamagata lineage viruses after March 2020, WHO considers the risk of infection by this lineage as low.[18] As a result, WHO no longer updates recommendations for the B/Yamagata lineage.[18]

Due to antigenic drifts and shifts which result in changes in the circulating virus strains, the influenza vaccine must be administered annually.[6,10,17] Additionally, vaccine effectiveness gradually wanes over time which further necessitates annual vaccination.[6,8,17] The vaccine is suitable for persons aged ≥ 6 months and should ideally be administered very early, before the start of the influenza season, to allow sufficient time for adequate development of protective antibodies.[17] The recommended influenza vaccine dosages and administration schedules are shown in Table I.

Priority groups and recommendations for influenza vaccination

Certain population groups such as older adults (≥ 65 years), infants, pregnant women, immunosuppressed individuals (e.g. living with HIV; receiving chemotherapy or steroid treatment) and individuals with long-term chronic medical conditions (e.g. chronic cardiac, pulmonary, renal, metabolic, neurodevelopmental, liver or haematological diseases), are most vulnerable to severe influenza outcomes and should therefore be prioritised for annual vaccination.[3,5,6,21] Persons at increased risk of occupational exposure or transmission, particularly healthcare professionals and caregivers, should also be prioritised to protect both themselves and vulnerable patients.[22] See Figure 1 for further details.

The recipient's age, immunological status, and the match between the vaccination strain and the circulating strain may all potentially affect influenza vaccine effectiveness.[17] Influenza vaccine effectiveness is lower amongst older adults due to increasing age and impaired immune function.[6,10] However, influenza vaccination is highly recommended for older adults as it significantly lowers hospitalisation and death rates.[6,23] Furthermore, influenza vaccination has been shown to protect against influenza cardiovascular complications (e.g. myocardial infarction, myocarditis and stroke) and may protect against dementia.[24-26]

High influenza vaccine coverage is essential to ensure individual and community protection, known as herd immunity.[27,28] Herd immunity is a form of indirect immunity that occurs when a substantial proportion of the population is vaccinated, thereby reducing the likelihood of the unprotected being exposed to infected individuals.[28] The unprotected includes the unvaccinated (i.e. babies < 6 months of age and anyone who is allergic to the vaccine or a vaccine component) and those who have been vaccinated but are unable to mount an immune response (i.e. the immunocompromised); those exposed to a different strain of the influenza virus not targeted by the vaccine they received; and those who received a vaccine that had lost potency because of incorrect storage.[28]

Table I: Recommended dosage and dosage administration for IIV[6,19,20]

Age group	Children 6 months – 2 years	Children 3 years – 8 years	Adults and children ≥ 9 years
Vaccine	Trivalent IIV e.g. Influvac®		
Dose	Consult package insert 0.25 ml	0.5 ml	0.5 ml
Number of doses per annum	First year of vaccination: Two doses administered ≥ 1 month apart Subsequent seasons: Single dose	First year of vaccination: Two doses administered ≥ 1 month apart Subsequent seasons: Single dose	Single dose annually
Route of administration	Intramuscular		
Site of administration	Left anterolateral thigh or upper arm (deltoid muscle if muscle mass is adequate)	Left upper arm (deltoid muscle)	
Precautions	Do NOT administer by intravascular injection and ensure that the needle does not penetrate a blood vessel		

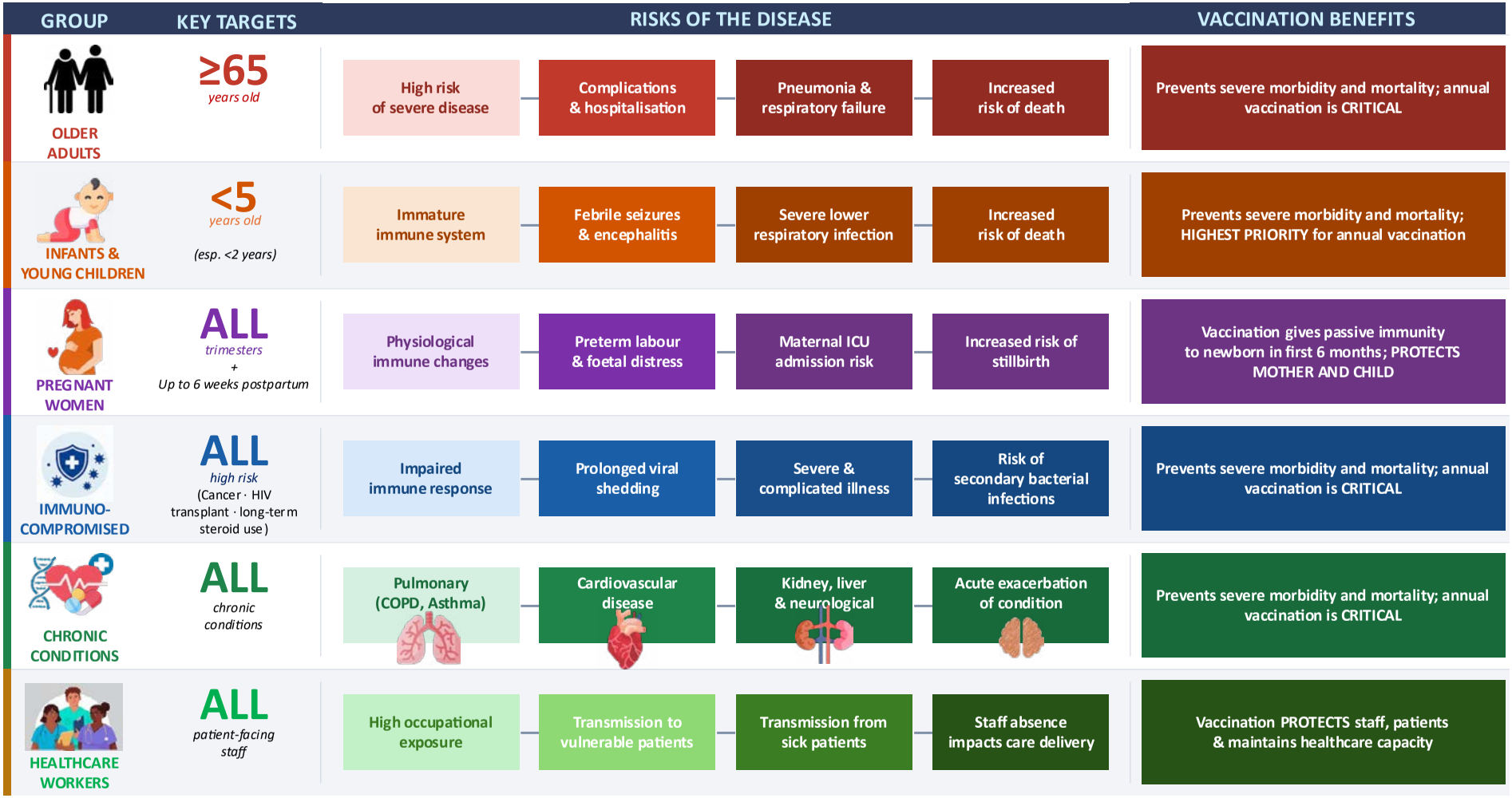

Figure 1: High-risk and priority groups for influenza vaccination[3,5,6,21]

Role of the pharmacist

Pharmacists as vaccine advocates

Pharmacists are among the most accessible healthcare professionals and are often the first point of contact within the health system for most people, particularly where other primary health services are inaccessible or too expensive.[29,30] In addition, pharmacies can reach more patients since they are usually conveniently located, have longer operating hours and patients can access pharmacy services without the need for making appointments.[29,30]

Pharmacists' easy accessibility positions them as ideal vaccine advocates, with the ability to reinforce preventive behaviours during patient interactions and to promote a broader culture of infection prevention within communities and healthcare settings.[29-31] In addition, pharmacists are key, accessible change agents in improving life-course immunisation (vaccination coverage across all life stages).[30,31] Through advocacy, education on the importance of vaccines in disease prevention and reducing AMR, and by direct administration of vaccines, pharmacists are well-positioned to help close vaccination gaps for children, adolescents and adults, by building vaccine confidence and improving vaccine access.[30]

The WHO Strategic Advisory Group of Experts on Immunization (SAGE) also emphasises the importance of healthcare professionals, including pharmacists, in building public vaccine confidence.[32] Studies show that healthcare professionals recommendation is one of the key factors driving vaccine acceptance.[22,33] Conversely, it has also been shown that a lack of healthcare professionals recommendation may result in public complacency towards vaccination.[34] In 2022, the NICD launched CoughWatchSA, a digital participatory surveillance platform for influenza-like illness in South Africa.[35] CoughWatchSA aims to provide an early warning system for influenza-like illness outbreaks, enabling the early detection of the onset of the influenza season and supporting the public health community to implement timely interventions and mitigation strategies.[35] Pharmacists can contribute to this initiative by promoting it to their patients and by directly reporting the number of cases presenting at pharmacies with influenza-like illnesses and number of clients vaccinated against influenza using the online portal: https://coughwatchsa.org.za/.

Vaccine supply chain and cold chain management

Pharmacists play a critical role in ensuring the continuous availability, quality, and integrity of influenza vaccines throughout the supply chain.[30,36] Their responsibilities include appropriate procurement, stock management, and ensuring that vaccines are transported, received, and stored in accordance with Good Pharmacy Practice (GPP) standards.[36,37] Influenza vaccines should be stored in a dedicated vaccine refrigerator maintained between 2 °C and 8 °C, equipped with a continuous temperature monitoring device, and packed correctly to allow adequate cold air circulation.[36]

The South African National Department of Health (NDoH) has established public-private sector service level agreements (SLAs) for selected Expanded Programme on Immunisation of South Africa (EPI-SA) vaccines, whereby immunisation coverage is increased through supplying these vaccines to participating private pharmacies at no cost.[36,38] Although influenza vaccines are currently not included in the SLAs, this noteworthy model has been an effective mechanism for expanding access to EPI-SA vaccines.[36] The NDoH is currently reviewing this model with the aim of implementing a policy to improve access to all vaccines available in the public sector, including influenza vaccines.

Ensuring patient safety

Pharmacists can contribute to increasing public confidence in influenza vaccination through their involvement in vaccine safety monitoring. Influenza vaccines are safe and well-tolerated, with mild, self-limiting AEFI being common, while serious AEFI are extremely rare. The benefits of vaccination in preventing severe influenza, complications, hospitalisation and death far outweigh these risks.[17] Pharmacists are well-positioned to explain this benefit-risk balance to patients and to address misinformation that may contribute to loss of vaccine confidence.[36]

In South Africa, all vaccines are subject to strict regulatory oversight and must be registered by the South African Health Products Regulatory Authority (SAHPRA) before use. In addition, vaccine batches entering the country go through rigorous quality control processes before release by SAHPRA, providing further assurance of vaccine safety, quality, and effectiveness.[39,40]

The vaccine is contraindicated for persons with a history of severe anaphylaxis following influenza vaccination, and caution should be exercised in persons with a history of Guillain-Barré syndrome within six weeks of influenza vaccination.[6] The vaccine should preferably be withheld from persons with moderate or severe illness with or without fever, until the symptoms have resolved.[6] Within the pharmacy setting, pharmacists should assess patients for any contraindications and precautions before vaccination, including a history of severe allergic reactions to vaccine components or previous influenza vaccines.[16,40] Pharmacists should also ensure correct storage conditions and check expiry dates as part of vaccine safety assurance. Where pharmacists administer vaccines, they should follow recommended administration procedures and must be prepared to recognise and manage immediate AEFI, including anaphylaxis.[41]

Pharmacists, as part of their practice, should contribute to pharmacovigilance through the identification, documentation, and reporting of AEFI.[39] Timely reporting of suspected AEFI to SAHPRA through the VigiMobile App (available online at: https://vigiflow-eforms.who-umc.org/za/aefi) supports ongoing vaccine safety monitoring and helps detect rare or unexpected AEFI.

Pharmacists as vaccinators

As custodians of medicines, pharmacists are focussing on the provision of safe and effective medicines.[29,31] Lately, pharmacist-

led immunisation is expanding throughout the world, and pharmacists are now playing an even greater role in disease prevention by advocating for and administering vaccinations.[29,31] In South Africa, the COVID-19 pandemic accelerated this role, leading to the country's largest public-private-partnership to date, in which community pharmacies collaborated with the NDoH to support the national COVID-19 vaccine rollout.[41,42]

According to Regulation 18(6)(b) of the regulations relating to the practice of pharmacy and Rule 2.14 of the rules relating to GPP, pharmacists may participate in immunisation-related activities, including the actual administration of vaccines to members of the public, as a part of their scope of practice provided they are authorised to do so and possess a Section 22A (15) permit.[41,42] Furthermore, the South African Pharmacy Council has developed competency standards for pharmacists providing immunisation services, defined the scope of practice for pharmacists offering such services, and established criteria to accredit a generic short course for pharmacists in immunisation and injection techniques, and the delivery of immunisation services.[41,42] Currently, four universities offer a short course for pharmacists in immunisation and injection techniques, upon successful completion of which pharmacists are certified as vaccinators.[43]

Conclusion

Influenza vaccination remains the most effective influenza prevention strategy and should be included in vaccination across the life-course. Influenza vaccines are also key in combating AMR. Despite the availability of safe and effective vaccines, vaccine uptake is suboptimal due to many factors, including access barriers and low vaccine confidence. This has the effect of increasing morbidity and mortality, which in turn imposes a heavy socioeconomic burden on the country. Pharmacists and other healthcare professionals have a key role to play in increasing vaccine uptake by ensuring the availability and correct storage of vaccines, providing immunisation services and advocating for vaccines, and educating clients on the risks of the illness and the benefits of the vaccines, thereby building vaccine confidence. In addition, they should inform clients about vaccinations provided at no cost through public health programmes to reduce barriers to access and thus improve vaccine coverage. As South Africa has already entered the 2026 influenza season, pharmacists are urged to serve as vaccine "champions" by strengthening vaccine confidence, actively countering misinformation related to influenza and other vaccines, and providing high quality vaccination services.

ORCID

M Sibanda https://orcid.org/0000-0002-9753-5284
M Munzhedzi https://orcid.org/0000-0003-1082-0881
Z Ismail https://orcid.org/0000-0001-7794-4649
RJ Burnett https://orcid.org/0000-0003-1346-1570
JC Meyer https://orcid.org/0000-0003-0462-5713

References

1. Luliano AD, Roguski KM, Chang HH, et al. Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. Lancet. 2018;391(10127):1285-300.
2. Shao C, Huang X, Zhang H, et al. Global, regional, and national burden of influenza-associated lower respiratory infections, 1990-2021: a systematic analysis from the Global Burden of Disease Study 2021. BMC Infect Dis. 2026;26(1):255. https://doi.org/10.1186/s12879-025-12282-7.
3. World Health Organization. Seasonal influenza - Global situation. Disease Outbreak News. 10 December 2025. Available from: https://www.who.int/emergencies/disease-outbreak-news/item/2025-DON586.
4. Statistics South Africa. Mortality and causes of death in South Africa, 2023: Findings from death notification. Statistical Release P0309.3. Pretoria: Statistics South Africa; 2026. Available from: https://www.statssa.gov.za/publications/P03093/P030932023.pdf. Accessed 6 April 2026.
5. Tempia S, Walaza S, Moyes J, et al. Quantifying how different clinical presentations, levels of severity, and healthcare attendance shape the burden of influenza-associated illness: a modeling study from South Africa. Clin Infect Dis. 2019;69(6):1036-48. https://doi.org/10.1093/cid/ciy1017.
6. Blumberg L, Cohen C, Dawood H, et al. Influenza: NICD recommendations for the diagnosis, management, prevention and public health response [Internet]. April 2026. Available from: https://www.nicd.ac.za/wp-content/uploads/2026/04/Influenza-guidelines_-10-April-2026.pdf. Accessed 30 April 2026.
7. National Institute for Communicable Diseases (NICD). Weekly respiratory pathogens surveillance report. Week 13, up to 29 March 2026. 2026a. Available from: https://www.nicd.ac.za/diseases-a-z-index/disease-index-covid-19/surveillance-reports/weekly-respiratory-pathogens-surveillance-report-week/. Accessed 27 April 2026.
8. Uyeki TM, Hui DS, Zambon M, Wentworth DE, Monto AS. Influenza. The Lancet. 2022;400(10353):693-706. https://doi.org/10.1016/S0140-6736(22)00982-5.
9. Wang CC, Prather KA, Sznitman J, et al. Airborne transmission of respiratory viruses. Science. 2021;373(6558). https://doi.org/10.1126/science.abd9149.
10. World Health Organization (WHO). Vaccines against influenza: WHO position paper - May 2022. Weekly Epidemiological Record, No 19, 2022, 185-208. Available from: https://www.who.int/publications/i/item/who-wer9719. Accessed 3 March 2024.
11. Boyles TH, Brink A, Calligaro GL, et al. South African guideline for the management of community-acquired pneumonia in adults. South Afr J Infect Dis. 2018;33(1):5-27. https://doi.org/10.4102/sajid.v33i1.22.
12. Blanchet Zumofen MH, Frimpter J, Hansen SA. Impact of Influenza and Influenza-Like Illness on Work Productivity Outcomes: A Systematic Literature Review. Pharmacoeconomics. 2023;41(3):253-73. https://doi.org/10.1007/s40273-022-01224-9.
13. Edoka I, Kohli-Lynch C, Fraser H, et al. A cost-effectiveness analysis of South Africa's seasonal influenza vaccination programme. Vaccine. 2021;39(2):412-22. https://doi.org/10.1016/j.vaccine.2020.11.028.
14. Fraser H, Tombe-Mdewa W, Kohli-Lynch C, et al. Costs of seasonal influenza vaccination in South Africa. Influenza Other Respir Viruses. 2022;16(5):873-80. https://doi.org/10.1111/irv.12987.
15. Brink A, Kgasi A, Musyoki A, et al. Vaccines in the fight against antimicrobial resistance - perspectives from South Africa. S Afr Med J. 2024;114(9):e2111.
16. Meyer JC, Sibanda M, Burnett RJ. Vaccination against influenza saves lives - A 2021 update. South Afr Pharm J. 2021;88(2):13-18. https://doi.org/10.36303/SAGP.2021.2.3.0075.
17. World Health Organization. Improved influenza vaccines: full value vaccine assessment. Geneva: World Health Organization. 2025. Licence: CC BY-NC-SA 3.0 IGO. Available from: https://www.who.int/publications/i/item/9789240117228. Accessed 6 April 2026.
18. World Health Organization. Recommended composition of influenza virus vaccines for use in the 2026 southern hemisphere influenza season [Internet]. World Health Organization. 2025. Available from: https://www.who.int/teams/global-influenza-programme/vaccines/who-recommendations. Accessed 21 February 2026.
19. National Department of Health, Essential Drugs Programme. Primary Healthcare Standard Treatment Guideline and Essential Medicine List. 8th ed. South Africa: National Department of Health. 2024. Available from: https://www.health.gov.za/nhi-edp-stgs-eml/. Accessed 27 April 2026.
20. Influvac® package insert. Abbott Laboratories S.A. (Pty) Ltd. 2020.
21. Tempia S, Walaza S, Moyes J, et al. Influenza disease burden among potential target risk groups for immunization in South Africa, 2013-2015. Vaccine. 2020;38(27):4288-97. https://doi.org/10.1016/j.vaccine.2020.04.045.
22. Sibanda M, Meyer JC, Godman B, Burnett RJ. Low influenza vaccine uptake by healthcare workers caring for the elderly in South African old age homes and primary healthcare facilities. BMC Public Health. 2023;23(1). https://doi.org/10.1186/s12889-022-14926-8.
23. Sibanda M, Meyer JC, Mahlaba KJ, Burnett RJ. Promoting healthy ageing in South Africa through vaccination of the elderly. Front Public Health. 2021;9:635266. https://doi.org/10.3389/fpubh.2021.635266.
24. Bukhbinder AS, Ling Y, Hasan O, et al. Risk of Alzheimer's disease following influenza vaccination: A claims-based cohort study using propensity score matching. J Alzheimers Dis. 2022;88(3):1061-74. https://doi.org/10.3233/JAD-220361.
25. Lee KR, Bae JH, Hwang IC, et al. Effect of influenza vaccination on risk of stroke: A systematic review and meta-analysis. Neuroepidemiology. 2017;48(3-4):103-10. https://doi.

Full list of references available on request

Human papillomavirus in cancer: Pathogenesis and vaccination approaches

M Maré, M Balmith

Department of Pharmacology, Faculty of Health Sciences, University of Pretoria, South Africa
Corresponding author, email: marissa.balmith@up.ac.za

Abstract

Human papillomavirus (HPV) is a small, non-enveloped virus that infects cutaneous and mucosal epithelium. It is sexually transmitted, and persistent infections with high-risk strains, such as HPV-16 and HPV-18, have been identified as contributing factors to 70% of global cervical cancer cases. Cervical cancer is a serious problem in developing countries such as South Africa, where early detection of precancerous lesions and comorbidities remains a challenge. The oncogenic activity of high-risk HPV strains is driven by the overexpression of E6 and E7 oncoproteins that bind to and inactivate key cell cycle regulators in host cells, such as tumour suppressor protein p53 and retinoblastoma protein (pRb), resulting in the transformation of normal cells into cancerous cells. Since cervical cancer is a global health problem, vaccines that prevent and target HPV infections have been developed to eliminate HPV-related cancers. Prophylactic vaccines are based on virus-like particles derived from genotype-specific L1 proteins and are essential for preventing HPV infections by inducing neutralising antibodies. School-based vaccination programmes in South Africa provide a single-dose of a L1-based bivalent vaccine, Cervarix, to girls over 9 years of age. While prophylactic vaccines prevent HPV infections, they have no therapeutic effect in patients with established infections. Therefore, therapeutic vaccines, such as ADXS11-001 and MVA-E2, which induce cell-mediated immune responses against viral oncoproteins E6 and E7 in HPV-related cancer, are currently under clinical investigation worldwide. The types of therapeutic vaccines that have been developed and evaluated in clinical trials include vector-, peptide- and protein-, whole-cell-, and nucleic acid-based vaccines; however, none have been approved for clinical use. Improving the efficacy of prophylactic and therapeutic vaccines remains critical for targeting HPV-related cancers.

Keywords: cancer, human papillomavirus, infection, vaccines

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Introduction

The human papillomavirus (HPV) infection is the most common sexually transmitted infection worldwide. In 2022, an estimated 1 505 394 HPV-related cancer cases and 755 303 deaths were reported globally.[1] Although HPV infection is more common in women, with an estimated 80% of women contracting HPV by the age of 50, it can be contracted by sexually active men and women.[2] Geographically, there are significant differences in HPV infection rates, with developing nations exhibiting a higher prevalence of new infections and mortality than developed nations.[1] The region with the highest incidence of HPV-related cancer is sub-Saharan Africa (SSA) with 120 000 cases reported in 2018, and a disproportionate number of young South African women (< 25 years) being affected.[3,4] The high burden of HPV-related cancer in SSA is likely due to the high cost of co-financing vaccines subsidies, inadequate infrastructure for vaccine cold-storage, logistical issues when transporting large quantities of vaccines, vaccine hesitancy due to misinformation and a lack of education and limited access to screening programmes.[3,5,6] Despite companies such as Gavi (the Vaccine Alliance) subsidising HPV vaccines in 57 low-income countries, national HPV vaccination programmes are not yet universally available in countries such as Angola, Ghana, Namibia and Madagascar.[6,7]

Epidemiology and oncogenic classification of human papillomavirus

HPV is a non-enveloped deoxyribonucleic acid (DNA) virus that infects the skin and mucous membranes, with more than 200 different strains identified.[8] Currently, high-risk HPV strains responsible for the majority of HPV-related cancers include HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66, and -68. Furthermore, HPV-16, -18, -31, -33, and -58 are commonly identified in cervical cancer, with HPV-16 and -18 responsible for more than 70% of all cervical cancer cases.[9] In contrast, low-risk HPV strains, such as HPV-6 and -11, induce genital warts and papillomatosis of the larynx.[10] Most HPV infections are asymptomatic and transient; however, if spontaneous clearance of the virus does not occur, persistent infection (lasting more than 24 months) with high-risk HPV can result in precancerous lesions and ultimately lead to the development of various cancers over 15–20 years.[6,10] In immunocompromised individuals, such as human immunodeficiency virus (HIV)-positive women, the development of cervical cancer from an HPV infection is faster (5–10 years) and 6 times more likely compared to HIV-negative women.[6,11,12] If cancer is diagnosed early, it can be treated with surgery, chemotherapy or radiation, therefore, the prevention and early detection of HPV infections are essential to detect pre-cancerous lesions and reduce the risk of oncogenesis.[5,13]

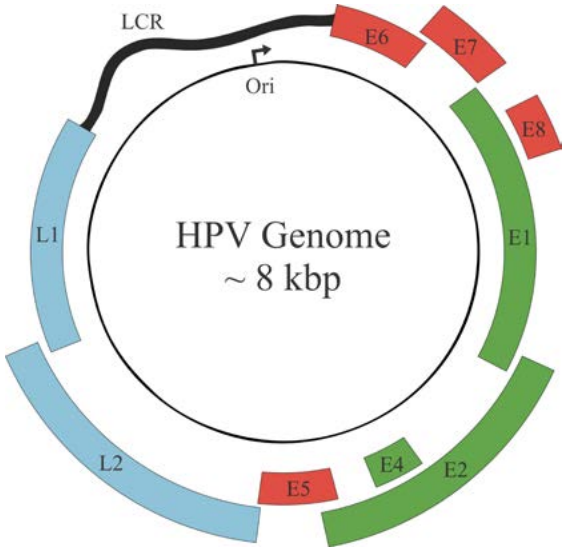

Figure 1: Human papillomavirus genome. HPV is a double-stranded DNA virus of approximately 8 kbp, consisting of early (E1-E8), late (L1 and L2), and long control regions (LCR). The early region includes genes essential for viral replication (green) and oncogenesis (red), whereas the late proteins are capsid proteins necessary for the formation of new virions.

Ori – Origin of replication, kbp – Kilobase pairs

Transmission and oncogenesis of human papillomavirus

HPV has a double-stranded circular DNA genome of approximately 8 kilobase pairs (kbp) encoding early (E) region proteins, late (L) region proteins, and an upstream regulatory region (URR) (Figure 1).[2,14] The early region encodes seven non-structural proteins linked to viral replication, namely E1, E2, E1^E4, E5, E6, E7, and E8^E2. The viral proteins E6 and E7 target several host oncogenic and tumour suppressor proteins such as p53 and pRB in the host cell.[14] Viral capsid proteins consist of L1 and L2 proteins and the URR, responsible for regulating DNA replication and is used for HPV classification.[2,14]

HPV transmission primarily occurs during sexual contact through skin-to-skin or skin-to-mucosa contact; however, non-sexual transmission, including indirect transmission via hands, perinatal transmission from mother-to-child and transmission via blood are also possible.[2,15] The HPV virus enters the basal layer of the epithelium through micro-wounds or micro-abrasions, and attaches to cellular receptors on the basal cells (Figure 2).[16] Entry of the HPV into host cells is facilitated through endocytosis when the L1 viral capsid protein attaches to heparan sulphate

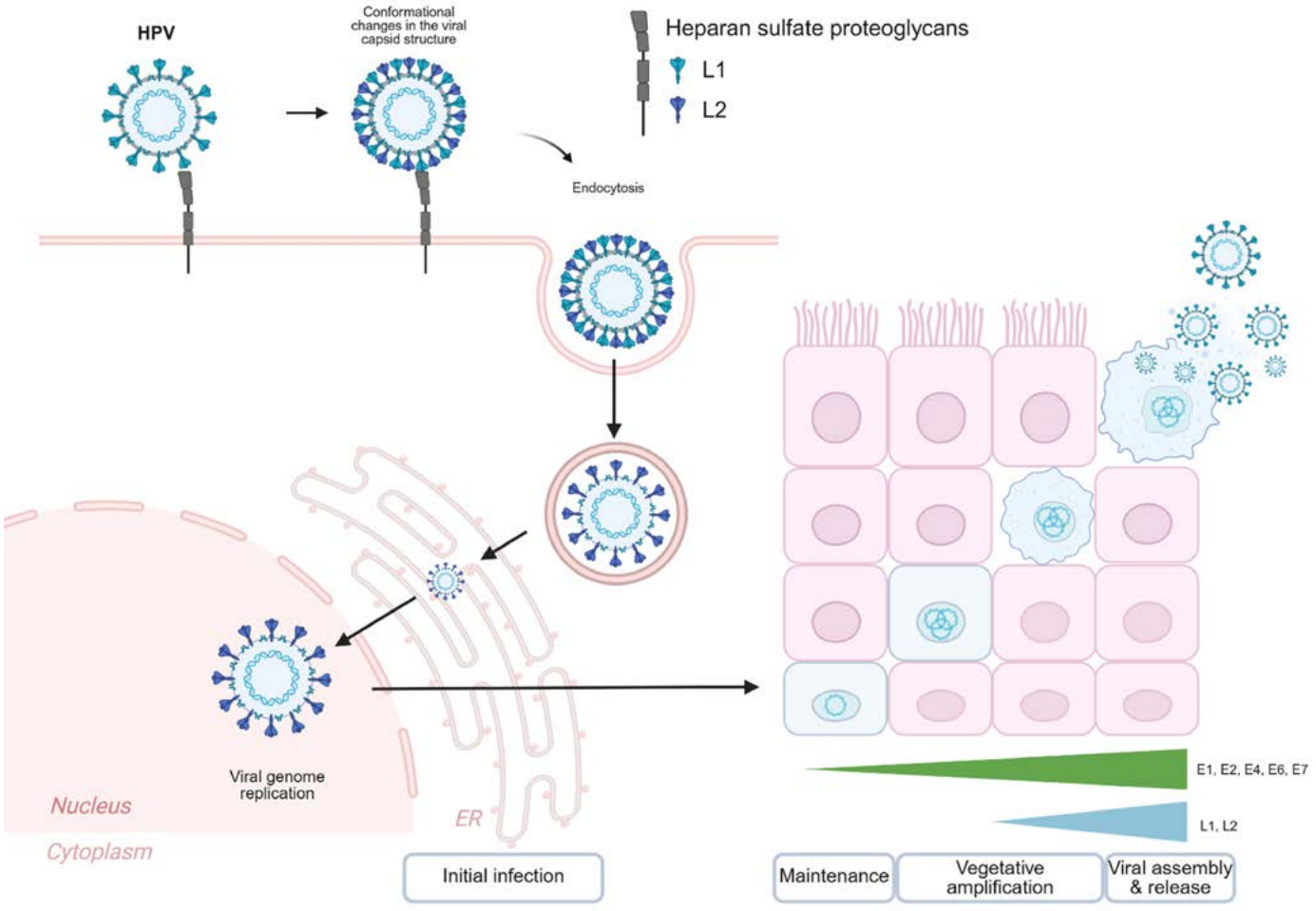

Figure 2: Lifecycle of high-risk HPV. HPV enters basal epithelial cells upon trauma and undergoes various stages: infection, maintenance, vegetative replication, viral assembly, and release. The virus binds to heparan sulphate proteoglycans through L1 capsid proteins. Subsequently, conformational changes expose L2 capsid proteins, and the viral particle is internalised into the host cell. The L2-DNA complex is delivered to the Golgi network, from where it enters the nucleus during mitosis. Early genes E1, E2, E4, E6, and E7 and late genes including L1 and L2 are expressed in stratified epithelial cells during infection, viral genome replication, and virion release. (Biorender, 2026)

proteoglycans.[16] This leads to conformational changes in the viral capsid structure, which expose the L2 capsid protein on the surface of the viral particle.[17] Next, the N-terminal of L2 is cleaved by proprotein convertase furin, which facilitates the transfer of the viral particle to a secondary receptor and results in subsequent internalisation.[18]

HPV infection undergoes four stages in its life cycle: initial, maintenance, vegetative amplification, and viral assembly and release.[5] Inside the host basal cell, the viral particle travels within endosomes, where the viral capsid is disassembled in a low pH environment. From there, the L2-related viral genome is transported to the trans-Golgi network and ultimately released in proximity to the host nuclear membrane.[19] Entry of the L2-viral genome complex into the nucleus occurs during early mitosis when the nuclear envelope is disrupted.[20] Once inside the nucleus, viral genome replication depends on host DNA replication machinery, and E1 helicase and E2 proteins which initiate viral genome replication are expressed.[21] In high-risk HPV strains, the expression of E6 and E7 promotes cell cycle progression and prevents apoptosis, as these oncoproteins bind to the host p53 tumour suppressor protein and the cell cycle regulator protein pRb, respectively.[22] During the initial infection phase, a low copy number (50–100 per cell) of the viral genome is generated as genome amplification is inhibited by the interaction of host nuclear receptor corepressor and silencing mediator for retinoid and thyroid hormone receptors (NCOR/SMRT) complexes with E8^E2C proteins.[8] Thereafter, the maintenance phase is initiated, and a constant number of viral genomes exist as extrachromosomal plasmids in the undifferentiated basal cells to create a persistent infection.[23] Normally, when daughter cells detach from basal cells, there is a loss of nuclei as cell proliferation is inhibited; however, HPV-infected cells remain active in the cell cycle due to the E7 protein.[22] Therefore, vegetative amplification of the viral genomes occurs in differentiated keratinocytes of the stratified epithelium and produces thousands of viral genomes. Additionally, capsid proteins L1 and L2 are expressed, which results in the assembly and release of newly formed virions during desquamation of the outer layers.[22] The time taken from initial infection to the production of new virions is at least 3 weeks, since this is the time taken for basal cells to differentiate, migrate to the epithelium surface and desquamate.[24]

Most HPV infections are resolved on their own through the cell-mediated immune system; however, persistent infection with high-risk HPV can lead to the integration of part of the viral genome within the host genome, facilitating the development of cancer. Integration of the viral genome typically results in the overexpression of oncoproteins E6 and E7.[25] Unregulated expression of E6 and E7 interferes with the functions of tumour suppressor genes, such as p53 and pRB, respectively. In normal cells, p53 detects DNA damage and inhibits cell proliferation to allow for DNA repair or cell apoptosis; however, E6 interaction results in p53 degradation and ultimately genome instability.[26] The retinoblastoma protein and structurally related p107 and p130 proteins regulate cell cycle progression by binding and inhibiting E2F transcriptional factors that regulate the expression of genes necessary for DNA synthesis and cell division. However, high-risk HPV E7 proteins target pRB and related proteins for protein degradation, which releases E2F transcription factors and results in the expression of genes necessary for cell cycle progression.[27] Ultimately, this results in the uncontrolled growth of infected cells.

Therefore, long-term persistent infection with high-risk HPV results in cellular alterations and precancerous lesions that, if left untreated, could develop into cancer. Viral genome integration and subsequent E6 and E7-mediated mutations are seen in 74% of HPV-16 and 100% of HPV-18 infected cervical carcinomas.[28] It is estimated that persistent high-risk HPV infections result in 6 types of cancers and cause 90% of cervical and anal cancers, 70% of vaginal, vulvar and oropharyngeal cancers and 60% of penile cancers.[5,29] These organs have interior surfaces lined with squamous cells that become infected with HPV.[2]

HPV infection and HIV co-infections contribute to cervical cancer oncogenesis due to the pronounced proliferative effects of viral oncoproteins E5, E6, and E7 in immunocompromised HIV-positive patients. Furthermore, immune response in patients co-infected with HPV and HIV, which consist of impaired T-cells and immature dendritic cells, is insufficient to clear persistent HPV infections.[30] HIV-infections also accelerate the progression of precancerous lesions to cervical cancer by inducing epithelial-mesenchymal transition, which facilitates cell growth and metastasis, through the activation of the canonical Wnt signalling pathway.[30] One of the main strategies to reduce the incidence of cervical cancer is routine screening for precancerous lesions that can be treated before progressing to cervical cancer.[12]

Screening and diagnosis of HPV-induced lesions

A persistent high-risk HPV infection can result in precancerous lesions; therefore, early diagnosis and regular screening are essential to stop the development of cancer.[2,5] Various methods are available to detect precancerous changes in the form of lesions in cervical cells.

Cytological strategies have been implemented to identify precancerous lesions formed due to HPV infections, such as the Papanicolaou (Pap) smear, colposcopy, visual inspection test with acetic acid (VIA), and thin prep cytologic test (TCT). For cervical cancer, which has the fourth highest mortality rate in women with approximately 350 000 deaths in 2022, Pap smears are routinely used to detect aberrant cells, which could be a sign of precancerous lesions. However, the Pap smear has low specificity and sensitivity, and may result in inaccurate results.[31] Alternatively, colposcopy helps identify precancerous lesions that are imperceptible to the naked eye, improving the accuracy of histological sampling and diagnosis.[32] The visual inspection test with acetic acid has a higher specificity than the Pap smear, as an acetic acid solution can be applied directly to the cervix to detect underlying pathology. However, VIA has lower accuracy in menopausal women, and a higher rate of false positives is observed.[33] Finally, TCT is a liquid-

based cytological screening method that is more effective than Pap smear in detecting abnormal cervical cells and facilitates early detection and prevention of cervical cancer.[34]

Additionally, HPV screening methods, such as Hybrid Capture 2 (HC2) and Polymerase Chain Reaction (PCR)-based HPV screening, have been developed to reduce the false negatives observed with cytological screening. Hybrid capture 2 is an HPV test that consists of a probe that detects HPV infections from 13 high-risk strains; however, single strains cannot be identified, and a minimum of 5 000 viral copies are needed for a positive result.[35] Polymerase chain reaction-based screening detects HPV-DNA or messenger ribonucleic acid (mRNA) with high sensitivity from few viral copies, allowing for the detection of numerous HPV strains or the active transcription of E6/7, respectively.[36,37] HPV screening detects cervical cancer earlier than cytological screening, making it superior to cytological screening (Pap smear and VIA test), which could influence the prognosis of cancer.[12,38]

The guidelines for HPV screening from the World Health Organization (WHO) and Centres for Disease Control and Prevention (CDC) include routine screening for women only, as no tests are approved for screening men. If the Pap smear is negative, re-evaluation is recommended every 3 years for females aged 21–30 years, and Pap smear with PCR-based HPV testing is recommended every 3–5 years for females aged 30–65 years.[5,29] Lesions detected in the epithelium of the cervix have been classified into three groups: cervical intraepithelial neoplasia (CIN) 1–3. Low-grade CIN1 refers to flat warts that can produce newly formed viral particles, with low proliferation at the bottom third of the epithelium. High-grade CIN2 lesions consist of infected basal cells occupying two-thirds of the epithelium, while high-grade CIN3 lesions are precancerous.[2] Depending on the classification, women may undergo surgery to remove precancerous lesions. The prognosis for HPV infection remains good, as spontaneous clearance of the virus occurs within 12–24 months. However, 10% of HPV infections persist and can progress to cancer, which has a high mortality rate.

Preventative and therapeutic management of HPV-infections

Currently, there is no treatment for HPV infections; however, prophylaxis is available to prevent infection and subsequent cancers. Therefore, the WHO launched a global strategy to eliminate cervical cancer as a public health problem by 2030, built around the 90-70-90 targets for vaccination, screening, and treatment: 90% of girls aged 15 years vaccinated, 70% of women aged 35–45 screened for HPV infections, and 90% of women with precancerous lesions and cervical cancer treated.[39] Cervical cancer is primarily prevented through HPV vaccination and secondarily through screening for the symptoms and diseases caused by HPV infection, such as warts and cancer.

Prophylactic vaccines

The widespread use of preventative vaccinations has significantly reduced the prevalence of HPV infections and related diseases, as they result in high levels of neutralising antibodies against specific HPV strains.[2,40] Currently, three main prophylactic HPV vaccines are available: bivalent, quadrivalent, and nonavalent (Table I).[41] The bivalent vaccine (Cervarix, Cecolin, Walrinvax) targets HPV-16 and -18, while the quadrivalent vaccine (Gardasil, Cervavax) targets HPV-6, -11, -16, and -18. In South African schools, the vaccination programme consists of a single dose of Cervarix administered to girls aged 9–15 years, with increased dosing for immunocompromised individuals. The most recent nonavalent vaccine (Gardasil 9), which has largely replaced the quadrivalent vaccine, provides broader coverage against HPV-6, -11, -16, -18, -31, -33, -45, -52, and -58.[41,42] The nonavalent vaccine targets HPV genotypes present in 90% of cervical, 23% of vulvar, 61% of vaginal, 21% of oropharynx, 25% of penile, and 79% of anal cancer cases.[43] However, approximately 28% of HPV-infected individuals were infected with multiple genotypes, which frequently included high-risk HPV-16, -18, and -59, probable high-risk HPV-44, and low-risk HPV-82. Moreover, 64% of the cases with multiple HPV genotypes had at least one HPV genotype not covered by any of the existing bivalent, quadrivalent or nonavalent vaccines.[44]

Prophylactic vaccines consist of a non-infectious recombinant vaccine derived from the L1 capsid protein and result in sustained immunity against HPV infections for approximately 12 years by producing antigen-specific antibodies and activating B cell immunity.[29,45] Vaccines are developed in bacteria, yeast, or insect cells and administered with an adjuvant that induces high levels of antibodies and immune response. Due to the fact that vaccines are based on the L1 protein, they only provide strain-restricted immunity rather than broader genotypic coverage.[46]

The WHO recommends one or two doses of HPV vaccines for girls aged 9–14, one or two doses for girls and women aged 15–20, and two doses with a 6-month interval for women over 21.[9] Although vaccination is generally not administered to males in developing countries, the decrease in HPV infections in girls and young women due to vaccination coverage is expected to provide herd immunity to males.[46] However, global vaccination rates are low due to cost, restricted access and limited knowledge and only 30% of the global target and 31% of countries in Africa have full HPV vaccine coverage.[29,46] Pan-gender vaccination programmes, which include vaccination of adolescent boys and girls, have been implemented in various developed countries to prevent HPV transmission and protect against penile and anal cancers in men.[47]

Furthermore, various factors influence vaccine coverage and efficacy, such as vaccination age, geographical location, and education. Data suggest that HPV vaccines are highly effective when administered to HPV-naïve patients before they become sexually active, while vaccinations after HPV exposure have only approximately 50–60% efficacy against targeted HPV genotype-related lesions (CIN2 and CIN3) or cervical cancer.[48] Second, the types of HPV infections vary between geographical regions, with HPV-45 and -31 frequently detected in most regions except Asia, resulting in discrepancies in vaccine efficacy.[46] Finally, women's knowledge of HPV transmission and prevention increases the

Table I: Key features of globally available and licensed prophylactic HPV vaccines

Category	Mechanism of action	Name (Manufacturer)	Expression system	Eligibility and dosing schedule	Efficacy	Side effects	Clinical/ Experimental
Bivalent HPV-16 and -18[5,9]	L1 virus-like particle-based immunity targeting HPV-16 and -18[5,9]	Cervarix (GlaxoSmithKline)[47]	Baculovirus -Insect cell[5]	Males and females aged 9–14 years (1- or 2-dose schedule at 5–13 months apart) Males and females 15 years and older (3-dose schedule at 0, 1–2.5 and 5–12 months)[9]	70% protection against cervical cancer[46] Strong protection against oral HPV-16/18[46]	Injection site pain and swelling Systemic symptoms, such as fever, nausea, vomiting, dizziness, myalgia, and diarrhoea[46]	Food and Drug Administration (FDA), United States of America (USA) approved 2009[5,9]
	L1 virus-like particle-based immunity targeting HPV-16 and -18[5,9]	Cecolin (Xiamen Innovax Biotech Co., Ltd)[47]	*Escherichia coli*[5]	Females aged 9–14 years (2-dose schedule in 6-month intervals) Females 15 years and older (3-dose schedule at 0, 1–2 and 5–8 months)[9]	87.5% efficacy against high-grade cervical, vulvar and vaginal lesions[50]	Systemic symptoms include fever, nausea, vomiting, dizziness, myalgia, and diarrhoea.	National Medical Products Administration (NMPA)-China approved 2021[47]
	L1 virus-like particle-based immunity targeting HPV-16 and -18[5,9]	Walrinvax (Walvax, China)[47]	Yeast[5]	Females aged 9–14 years (2-dose schedule at 6-month intervals) Females 15 years and older (3-dose schedule at 0, 2–3 and 6–7 months)[9]	78.6% efficacy against high-grade cervical lesions[51]	Injection-site pain and swelling Systemic symptoms, such as fever, nausea, vomiting, dizziness, myalgia, and diarrhea[51]	NMPA-China approved 2022[5,9]
Quadrivalent HPV-6, -11, -16, and -18[5,9]	L1 virus-like particle-based immunity targeting HPV-6, -11, -16, and -18[5,9]	Gardasil (Merck & Co.)[47]	Yeast[5]	Males and females aged 9–13 years (2-dose schedule at 6-month intervals) Males and females 14 years and older (3-dose schedule at 0, 1–2 and 4–6 months)[9]	70–75% protection against cervical cancer[46] 90% and 80% protection against vulvar and vaginal diseases[46]	Injection-site pain and swelling[46]	FDA, USA approved 2006[47]
	L1 virus-like particle-based immunity targeting HPV-6, -11, -16, and -18[5,9]	Cervavac (Serum Institute of India)[47]	Hansenula polymorpha[5]	Males and females aged 9–14 years (2-dose schedule in 6-month intervals) Males and females 15 years and older (3-dose schedule at 0, 2 and 6 months)[9]	93% efficacy against persistent HPV-16/18 infection[52]	Injection-site pain, headache [53]	Drugs Controller General of India (DCGI) approved 2022[47]
Nonavalent HPV-6, -11, -16, -18, -31, -33, -45, -52, and -58 [5,9]	L1 virus-like particle-based immunity targeting HPV-6, -11, -16, -18, -1, -33, -45, -52, and -58[5,9]	Gardasil 9 (Merck & Co.)[47]	Yeast[5]	Males and females aged 9–14 years (2-dose schedule 6–12 months apart) Males and females 15 years and older (3-dose schedule at 0, 2 and 6 months)[9]	90% protection against cervical cancer[46]	Injection-site pain, dizziness, headache, syncope[54]	FDA, USA approved 2014[47]
	L1 virus-like particle-based immunity targeting HPV-6, -11, -16, -18, -31, -33, -45, -52, and -58[5,9]	Cecolin-9 (Xiamen Innovax Biotech Co., Ltd)[5,9]	*Escherichia coli*[5]	Females aged 9–17 years (2-dose schedule) Females 18 years and older (3-dose schedule)	Comparable immune response to Gardasil 9 after 3 years[55]	Injection-site pain and swelling, myalgia, fatigue, headaches[56]	NMPA-China approved 2025[57]

acceptance and initiation of vaccinations.[49] Therefore, to sustain higher vaccine coverage, educational initiatives are required.

Therapeutic vaccines

Therapeutic vaccines have been developed to treat cancers induced by high-risk HPV infections, aiming to generate cell-mediated immunity. These novel therapeutic vaccines target the E6 and E7 oncoproteins of high-risk HPV strains, which are the primary drivers of HPV-related oncogenesis.[2] Additionally, E2 could be an ideal drug target, as this protein acts as a translational repressor of E6 and E7 proteins. Four types of therapeutic vaccines have been developed and tested in genital neoplasia: vector-, peptide-, and protein-based, whole cell-based, and nucleic acid vaccines (Table II).[5]

Vector-based vaccines employ bacterial or viral vectors to deliver antigens and induce innate immune responses that mimic the natural course of infection. However, vaccine-related adverse effects, such as immune responses targeting the vector and high immunogenicity in patients with low immunity, limit the use of vector-based vaccines.[5,58] ADXS11-001, a vaccine composed of HPV-16 E7 carried by live-attenuated Listeria monocytogenes, resulted in a 34% overall survival in patients with refractory cervical cancer. Three vaccine-related serious adverse events were observed in phase II clinical trials and although phase III clinical trials were conducted, results have not been published.[59] MVA-E2, consisting of modified vaccinia viruses containing bovine E2 protein, had a 83% HPV DNA clearance rate and 89% overall efficacy in regression of CIN1 lesions.[60]

Peptide-based vaccines contain antigenic peptide segments, whereas protein-based vaccines are composed of antigenic proteins that are processed by dendritic cells and result in low T-cell immune responses.[58] Therefore, although these vaccines are safe, stable, and easy to produce, they are often combined with adjuvants to enhance immune response. ISA101, a peptide-based vaccine made of overlapping E6 and E7 proteins, was combined with CpG or GPI-0100 during phase II clinical trials and resulted in a polyclonal immune response that induces tumour regression in mice.[61] Furthermore, in patients with cervical cancer combination therapies of ISA101 and nivolumab resulted in a 33% response rate, while ISA101 and carboplatin-paclitaxel treatment resulted in tumour regression in 43% of patients.[62] However, patients with HPV-16 induced vulvar and vaginal precancerous lesions and advanced cervical cancer do not respond to ISA101 vaccines in combination with immune checkpoint blockades or chemotherapeutics.[62] The efficacy of PepCan, a peptide-based vaccine containing HPV-16 E6 peptides, was tested in phase II clinical trials resulting in a 45% regression rate in patients with high grade lesions.[63]

Whole-cell vaccines consist of dendritic cells that serve as adjuvants and are loaded with HPV E proteins. Dendritic cells loaded with HPV-16 and -18 E7 antigens were immunogenic in patients with CIN1/2; however, the manufacturing of whole-cell

Table II: Therapeutic vaccines targeting HPV

Type	Mechanism of action	Name	Eligibility (Dosing schedule)	Efficacy	Study phase
Vector-based[5]	Live-attenuated listeria monocytogenes containing HPV-16 E7 fused with listeriolysin O[59]	ADXS11-001[5]	High-risk advanced cervical cancer (3 doses at days 1, 29 and 57)[59]	Overall survival rate of 35% in 12 months[59]	Phase III[5,59]
	Vaccinia virus containing bovine HPV-16 E2 protein[60]	MVA-E2[5]	Intraepithelial CIN2/3 lesions (females: 6 weekly intralesional doses, males: 5 weekly intraurethral doses)[60]	83% HPV DNA clearance 89% elimination of CIN2/3 lesions in females 10% elimination of CIN2/3 lesions in males[60]	Phase III[5,60]
Peptide- or protein-based[5]	Nine E6 and four E7 HPV-16 derived peptides with Montanide ISA51 adjuvant[62]	ISA101[5]	HPV-16 solid tumours (two low-doses, 0 and 12 months)	Ineffective in patients with advanced cervical cancer	Phase II[5,62]
	HPV-16 E6 peptides and Candin adjuvant	PepCan[5]	High-grade cervical lesions (4 doses at a 3-week interval)[62]	Significant T-cell immunogenicity[62] Viral loads significantly decrease[62]	Phase I[5,63]
Whole cell-based[5]	Dendritic cells loaded with HPV-16 and -18 E7[64]	Antigen-pulsed mature dendritic cell[5]	CIN1/2 lesions (5 doses administered on days 0, 21, 42, 63 and 84)[64]	Significant T-cell immunogenicity[64]	Phase I[5,64]
Nucleic acid-based[5]	Two DNA plasmids encoding HPV-16 and -18 E6/7 proteins[65]	VGX-3100[5]	High grade cervical lesions (3 doses at weeks 0, 4 and 12)[65]	Virologic clearance at 18 months[65]	Phase IIb[5,65]
	Messenger- RNA encoding HPV-16 E6 and E7 proteins[66]	mHPV[5]	3 doses at 7-week intervals[66]	Significant T-cell immunogenicity[66]	Preclinical[5,66]

vaccines is labour-intensive and expensive, which limits their use.[58,64]

Lastly, nucleic acid vaccines contain bacterial plasmids or mRNA sequences and work by introducing genetic information encoding specific antigens into host cells. This allows the host cell to express antigenic proteins and activate an immune response against them. VGX-3100 contains synthetic DNA plasmids encoding HPV-16 and -18 E6 and E7 proteins. During phase II clinical trials, VGX-3100 efficiently induced HPV-16 and -18 viral elimination at 18 months following vaccination and resulted in regression of CIN3 lesions comparable to the control group, which underwent surgical treatment.[65] DNA-based vaccines are stable and safe, but have low immunogenicity, while RNA-based vaccines packaged into vectors that induce sustained T-cell responses are unstable.[5] Therefore, RNA-based vaccines, such as the mRNA-HPV (mHPV) vaccine encoding HPV-16 and -18 E6 and E7 proteins, are packaged into lipid carriers. Vaccination with mHPV effectively suppressed tumour growth in mice models and resulted in robust T-cell immune responses in mice and rhesus macaques.[66]

A variety of therapeutic vaccines that have been evaluated in phase II/III clinical trials resulted in an overall regression of 54% of CIN2/3 lesions. However, because this response rate is substantially lower than the efficacy achieved with standard surgical excision, none of the therapeutic vaccines have been approved for clinical use.[67,68] Although patients with persistent HPV infections after treatment remain at a higher risk of recurrence, the modest efficacy of the therapeutic vaccines in clinical trials may not justify replacing highly effective surgical interventions.

Strategies to increase global vaccination coverage

Future research is needed to develop financially feasible vaccines and improve vaccine formulations to produce high immunogenicity and broad-spectrum protection.[41,45] Current HPV vaccines, including bivalent and nonavalent vaccines, are stored at temperatures between 2 and 8°C, which could be a significant challenge in low-income countries with infrastructure and financial constraints. Several next-generation vaccines have been developed to facilitate vaccine access in low-income countries and provide broader protection against high-risk HPV strains and are candidates in advanced clinical trials.[57] These new vaccines include quadrivalent, nonavalent, 11-valent, and 14-valent L1-based formulations. Additionally, capsid protein L2-based vaccines, which allow long-term storage at room temperature and are broadly protective against various HPV strains, are under development. However, L2-based vaccine results in a low immune response and only provides protection for one year, therefore, various adjuvants, fusions and formulations are being explored to achieve a durable and adequate immune reaction response.[57]

Unlike prophylactic vaccines which prevent HPV infection, various therapeutic vaccines targeting E6 and E7 oncoproteins have been developed for cancer treatment. Multiple vector-, peptide- and DNA-based vaccines have established efficacy and immunogenicity, however, none have been licensed for clinical use.[42] These therapeutic vaccines have the potential to be used in combination with chemotherapy or radiation, and offer advantages such as disease-specific immune memory.[57]

Considering the high occurrence of HPV-related cancers in both men and women due to persistent HPV-infections, educational intervention and pan-gender vaccination programmes should be implemented globally to achieve better vaccination coverage.[46]

Conclusion

HPV infection is a global health concern strongly related to various malignancies, including benign lesions such as warts and life-threatening genital cancers. Persistent infection with high-risk HPV leads to the expression of E6 and E7 oncoproteins, which disrupt the cell cycle of squamous cells by enhancing cell proliferation and inhibiting cell apoptosis. Therefore, the WHO has launched a global strategy to eliminate HPV-related cervical cancer through vaccination and screening. Prophylactic vaccines developed and approved to prevent HPV infections include bivalent, quadrivalent, and nonavalent vaccines consisting of virus-like proteins from viral capsid protein L1 of different HPV genotypes. Despite the efficacy of prophylactic vaccines targeting high-risk HPV strains, vaccination coverage remains low, and more than 80% of cervical cancer mortalities occur in lower-income countries. Additionally, research on viral capsid protein L2 vaccines with broad genotypic protection is underway, and efforts to increase the low immunogenicity of these vaccines remain essential to provide protection against HPV genotypes not covered by L1 virus-like particle vaccines. Various therapeutic vaccines targeting viral oncoproteins E6 and E7 are being investigated for mono- and combination therapy in cancer treatment. Vector-, peptide- and protein-, whole-cell-, and nucleic acid-based vaccines have demonstrated immunogenicity against high-risk HPV genotypes and partial efficacy in lesion regression; however, none have been approved for commercialisation. As most studies involving therapeutic vaccines have been administered to patients with advanced cervical cancer, further research and clinical trials are warranted to validate and improve the efficacy and safety of therapeutic HPV vaccines.

Conflict of interest

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ORCID

M Maré https://orcid.org/0000-0003-0419-6218

M Balmith https://orcid.org/0000-0002-9209-7318

References

1. Meng X, Yang B, Yin H, et al. Global burden and incidence trends in cancers associated with human papillomavirus infection: A population-based systematic study. Pathogens. 2025;14(9):880. https://doi.org/10.3390/pathogens14090880.
2. Baba SK, Alblooshi SSE, Yaqoob R, et al. Human papilloma virus (HPV) mediated cancers:

Full list of references available on request

Overcoming vaccine hesitancy: An effective vaccine communication 'standard operating procedure' for pharmacists

JC Meyer[1,2] **RJ Burnett**[1,2]

[1] Department of Public Health Pharmacy and Management, Sefako Makgatho Health Sciences University, South Africa
[2] South African Vaccination and Immunisation Centre, Sefako Makgatho Health Sciences University, South Africa
Corresponding author, email: hannelie.meyer@smu.ac.za

Abstract

South Africa's Expanded Programme on Immunisation (EPI) coverage has been on a downward trend in recent years, contributing to outbreaks of vaccine-preventable diseases such as measles. While vaccine hesitancy is not a new phenomenon, its recognition as a major public health threat gained widespread recognition in the 21st century and was further exacerbated by the COVID-19 pandemic. In order to achieve the targets of Immunisation Agenda 2030 it is essential to address vaccine hesitancy through effective communication and behaviour change interventions. While pharmacists can play a critical role in engaging hesitant individuals, a clear understanding of the drivers of vaccination behaviour and the factors underlying declining vaccine confidence is necessary. This article proposes a practical, evidence-informed vaccine communication standard operating procedure to support South African pharmacists in their daily practice.

Keywords: vaccine hesitancy, vaccine communication, standard operating procedure

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Introduction

A 2024 study published in The Lancet found that between 1974 and 2023 (50 years), 154 million lives were saved by vaccinations against 14 pathogens targeted by the World Health Organization's (WHO) Expanded Programme on Immunisation (EPI).[1] This equates to 6 lives per minute being saved every day for 50 years, an astonishing achievement that is currently being undermined by widespread misinformation/disinformation leading to vaccine hesitancy. As a result, the world is not on track for reaching the WHO Immunisation Agenda 2030 (IA2030) goals, with vaccine coverage rates falling globally, placing millions at risk.[2] For example, global measles cases have surged because of low vaccine coverage, including in the United States of America (USA) and Europe, with measles predicted to become endemic in the USA if this declining trend in vaccine coverage continues.[3] Similarly, in South Africa EPI coverage has been on a downward trend for several years, resulting in outbreaks of vaccine-preventable diseases (VPDs) such as measles, rubella, diphtheria and pertussis.[4-6]

The vaccine hesitancy phenomenon

Vaccine hesitancy is an age-old phenomenon, originating after the cowpox vaccine against smallpox was invented in the late 18th century, and resurfacing after a fraudulent 1998 publication falsely claimed that the measles-mumps-rubella vaccine (MMR) caused autism.[7] While this article was subsequently retracted and the false claim thoroughly refuted by many subsequent studies, widespread media attention at that time resulted in continuous circulation that was later considerably amplified by the advent of social media.[7] Currently, anti-vaccination misinformation/disinformation social media campaigns are either directed against vaccines in general or target specific vaccines, while the vaccine misinformation/disinformation infodemic accompanying the coronavirus disease 2019 (COVID-19) pandemic has undermined trust in all EPI vaccines.[8]

Although vaccine hesitancy has existed for more than 250 years, it gained widespread recognition as a major public health threat only in the 21st century, being defined in 2014 by the WHO Strategic Advisory Group of Experts (SAGE) working group on vaccine hesitancy as a 'delay in acceptance or refusal of vaccination despite availability of vaccination services,'[9] and declared by the WHO as one of the top 10 threats to global health in 2019.[10] In terms of intervention design, a more helpful definition was coined in 2022 to exclude vaccine refusal and vaccine confidence, describing vaccine hesitancy as 'a state of indecision and uncertainty about vaccination before a decision is made to act (or not act)' (Figure 1).[10] This recognises vaccine denial as an unmodifiable fanatical state, whereas in essence, vaccine hesitancy as a state of being undecided about whether or not to vaccinate is open to behaviour change interventions. In order to achieve IA2030 goals, it is crucial to address widespread vaccine misinformation/disinformation leading to distrust of public health institutions as the major driver of vaccine hesitancy.[2] However, this is not something that will happen overnight, so right now, what can the South African pharmacist do to prepare themselves for effectively communicating with vaccine hesitant clients?

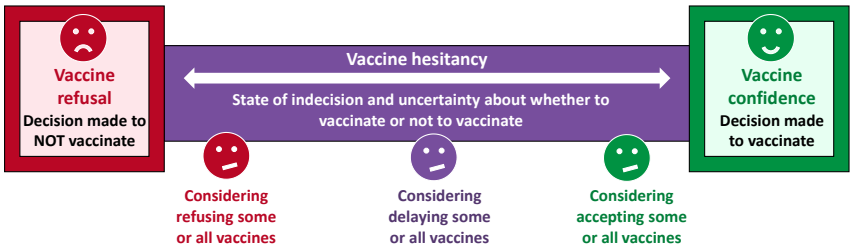


Figure 1: Spectrum of vaccine hesitancy

Preparation for effective communication with vaccine hesitant clients

Understand the drivers of vaccination behaviour

The drivers of vaccination behaviours are sometimes framed as the 3Cs: Confidence (in effectiveness, safety, the health system, policy makers), Complacency (perceived low risk of acquiring VPDs) and Constraints (barriers to accessing vaccination services, including time, place, language, and cultural contexts). They can also be framed as the 5Cs, when in addition to the 3Cs, Collective responsibility (understanding the value of vaccination for creating herd immunity) and Calculation (seeking information weighing the benefits and risks of vaccination) are also included (Figure 2).[11]

In addition, a qualitative evidence synthesis of global studies conducted by South African scientists, has suggested that these drivers are processed differently according to an individual's own worldview, following two potential pathways towards vaccine acceptance, namely 'neoliberal logic' and 'social exclusion'.[12] Neoliberals, who are mainly from high-income countries, believe they must assess their own health-related risks and make their own health-related decisions,[12] which conflicts with the concept of a 'social contract' where everyone is called upon to contribute towards herd immunity. In contrast, those experiencing social exclusion (i.e., economically, socially or politically), mainly from low- and middle-income countries, may lack trust in the government and may feel alienated, resentful, frustrated and demotivated.[12] Both of these pathways may lead to vaccine hesitancy or vaccine refusal, with neoliberals potentially being strongly influenced by misinformation leading them to reject vaccination based on their own faulty risk-benefit analysis, while the socially excluded may reject vaccination based on distrust of health authorities.

Understand how and why vaccine confidence is on the decline

The infodemic accompanying the COVID-19 pandemic, plus the often clumsy and sometimes inappropriate pandemic responses by many governments throughout the world, has severely eroded global public trust in vaccines in general, including in South Africa.[8,13] When South Africa started rolling out the COVID-19 vaccine in early 2021, it was eagerly anticipated by > 70% of adults who were planning to get vaccinated.[14] However, by January 2023 only 50% of South Africans had been vaccinated.[15] In 2023, the United Nations Children's Fund (UNICEF) reported a 30% decline in confidence in childhood vaccines in South Africa, with only 62% of South Africans being confident that vaccines are important for children.[13] Also in 2023, only 34% and 57% of South African adults respectively, were confident that the next pandemic would be handled better than the COVID-19 pandemic, and would be willing to be vaccinated against the disease causing the next pandemic.[8] Another 2023 study reported that 71% of South African adults' vaccination behaviours were found to fit the 2014 WHO SAGE definition of 'a delay in acceptance or refusal of vaccines despite the availability of vaccination services'.[9] While the COVID-19 pandemic ended in May 2023, the passage of time has not improved vaccine confidence, with a survey conducted in late 2024 finding that only 63% of all South African adults and 55% of South Africans aged 18–34 respectively, would give their children all recommended vaccines.[16] Unfortunately, many South African healthcare workers (HCWs) also fell prey to COVID-19 vaccine misinformation. For example, a survey conducted amongst Cape Town HCWs at the time the vaccine was being rolled out, 48% of whom were degreed healthcare professionals, reported that 41% would either refuse or hesitate to be vaccinated.[17]

Understand the reasons why some people may be vaccine hesitant

A study on vaccine sentiment expressed on South African social media platforms before the COVID-19 pandemic, reported that

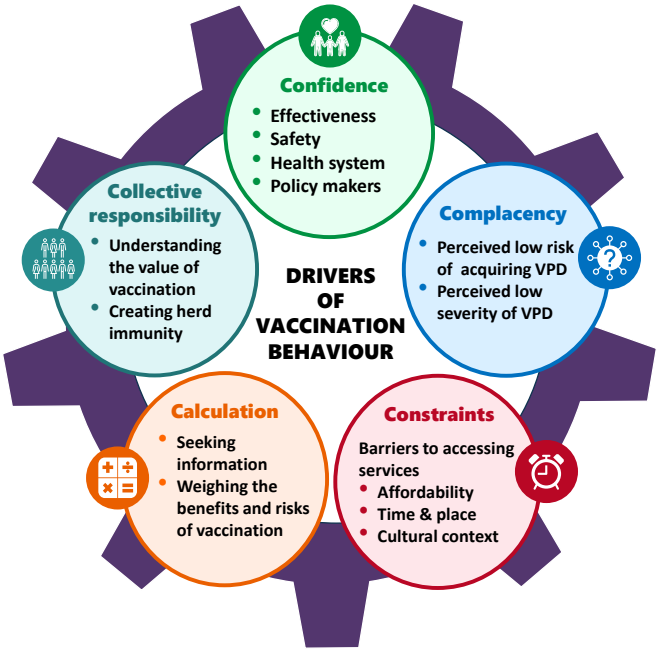


Figure 2: Drivers of vaccination behaviour

negative sentiments expressed vaccine safety concerns (including the beliefs that vaccines contain toxins that damage the brain/immune system/reproductive system; or cause cancer or death; and too many vaccines received simultaneously overwhelm the immune system); the belief that vaccines are not effective; belief in conspiracy theories (including being used as 'germ warfare' to 'depopulate the world'; and that the vaccine industry is solely profit-driven); and philosophical/religious objections (including vaccine ingredients that conflict with religious beliefs; vegans' objections to the use of animal products in vaccines; and mandatory vaccination, which does not exist in South Africa, being a violation of human rights).[18] In March 2021, while COVID-19 vaccines were being rolled out to HCWs in South Africa, the South African Medical Research Council reviewed all South African COVID-19-related surveys.[19] Similar to the pre-COVID-19 era, concerns about side effects, lack of effectiveness and conspiracy theories were reported. However, safety concerns included the newness of the vaccine, the speed at which it was developed and lack of trust in the government to ensure safety; while conspiracy theories included that COVID-19 is man-made and linked to 5G. Many respondents were opposed to vaccination in general, and many felt that they were at low risk for COVID-19.[19]

Standard operating procedure (SOP) for effective vaccine communication in practice

While this SOP targets pharmacists who are authorised vaccinators, all pharmacists can use this guide for effective vaccine communication (Figure 3).

Presumptive approach to initiating a conversation

Research has shown that when initiating vaccine conversations, the 'presumptive approach' is strongly associated with vaccine acceptance.[20-22] This approach assumes that the client is accepting of vaccination, and uses language such as 'I see that Lebo is now 6 weeks old, so today we are going to administer the vaccines scheduled for 6 weeks of age'. In contrast, using the 'participatory approach' or 'elective approach', as if you expect vaccination to be a shared decision between you and your client, is strongly associated with vaccine delay or refusal.[20-22] For example, if you say 'I see that Lebo is now 6 weeks old. Should we vaccinate her with the vaccines scheduled for 6 weeks of age today?' Lebo's caregiver may assume that you are not so sure about the value of vaccination and may rather want to either postpone or refuse vaccination.

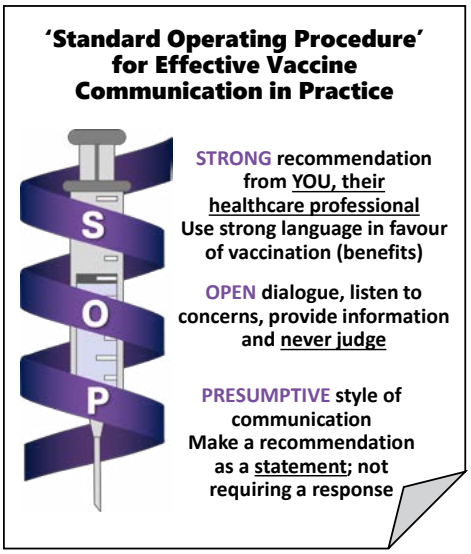


Figure 3: 'Standard Operating Procedure' for effective vaccine communication in practice

Open dialogue, listening and sharing information

When clients lack confidence in vaccines or perceive that vaccine side-effects are a greater risk to themselves/their children than the disease itself, they may decline vaccination. In this scenario, your immediate response should be what has been termed 'humble inquiry and compassionate listening'.[23] This response is supported by evidence from research on an intervention known as 'motivational interviewing,' the first steps of which are to enter into a trustful relationship with your client where they feel free to share their views without fearing judgement, allowing you to gain an understanding of exactly why they don't want to vaccinate themselves/their children.[24]

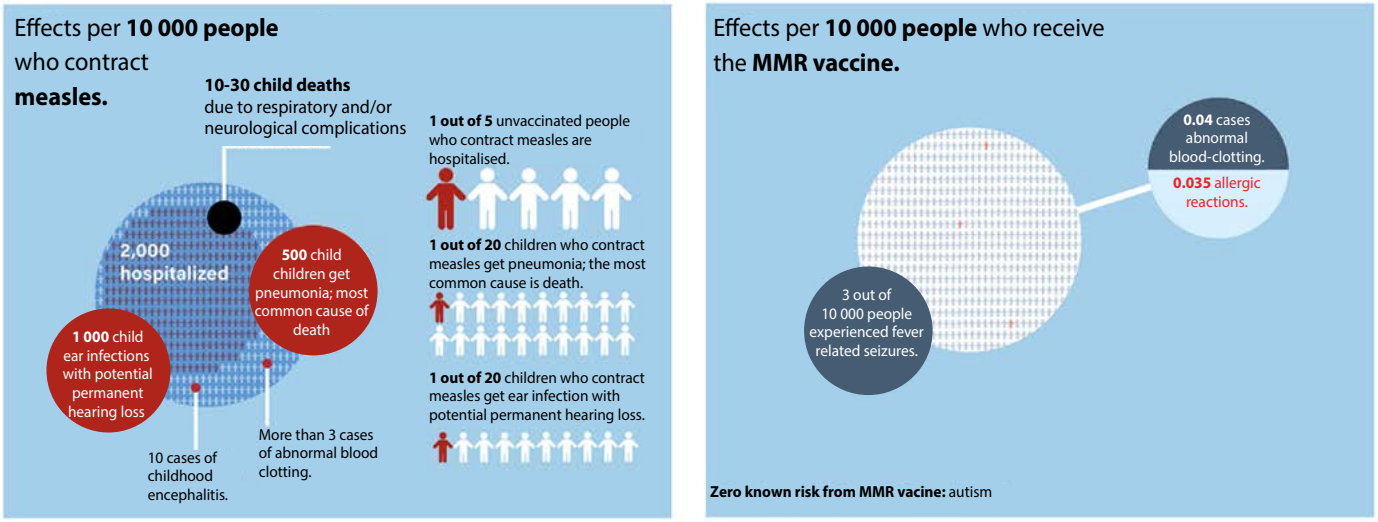
The next step is to offer information,[24] bearing in mind that transparency in providing information about the risk-benefit balance of vaccines shows respect for your client's autonomy[24] and builds trust.[26,27] While the emphasis should be on communicating scientific evidence and consensus on vaccine safety and effectiveness, acknowledging uncertainty and risk is also important for building trust and reducing vaccine hesitancy.[25-27] In addition, explaining the risks of the disease versus the risks of vaccine side effects with graphical aids as illustrated in Figure 4, has been shown to increase vaccine acceptance.[28] However, avoid fear-mongering or scare tactics, such as describing or showing photos of children with VPDs, as this may backfire and increase vaccine hesitancy.[26]

When debunking misinformation, use language that is easily understood by lay people, and avoid jargon and scientific terms.[29] Care must be taken to avoid strengthening belief in misinformation by needlessly repeating it, and always end the explanation with the fact; stating the fact at the end makes it easier to remember.[29]

Strong recommendation for vaccination

Furthermore, research has shown that strongly recommending vaccination is strongly associated with subsequent vaccine acceptance.[20-22] Also, communication emphasising the personal benefits of vaccination is strongly associated with vaccine acceptance.[26,27,30] In this regard, sharing your own personal stories of yourself or your family members being fully vaccinated and healthy, can be very powerful.[23,29]

Finally, while the above approach is highly likely to result in a happy ending, with your client accepting vaccination, if in the end your client is still reluctant to vaccinate, you need to respect



Comparing the risk of 10 000 children acquiring measles (left) versus receiving the measles-mumps-rubella (MMR) vaccine. A new original figure modified from.[9] Artwork by Fahim Akbar.[28]

Figure 4: Example of a graphical aid to explain VPD risks versus vaccine side effects risks[28]

their decision and leave the door open. This builds further trust, allowing the vaccination discussion to continue during future consultations.[24]

Conclusion

To recap, vaccine hesitancy, described as 'a state of indecision and uncertainty about vaccination before a decision is made to act (or not act),' is a major threat to global public health because it has resulted in a downward trend in vaccine coverage, resulting in VPD outbreaks. Understanding the drivers of vaccination behaviour, how and why vaccine confidence is on the decline and the reasons why people are vaccine hesitant, is important for communication and behaviour change interventions. Effective vaccine communication in practice should be based on three main principles: Initiate the vaccination conversation using the presumptive approach; provide a strong recommendation for vaccination highlighting personal benefits; and maintain open dialogue, listen, provide information and be non-judgemental. These principles have been summarised in Figure 3 and can be remembered as the SOP: Strong recommendation, Open dialogue and Presumptive approach.

ORCID

JC Meyer https://orcid.org/0000-0003-0462-5713

RJ Burnett https://orcid.org/0000-0003-1346-1570

References

1. Shattock AJ, Johnson HC, Sim SY, et al. Contribution of vaccination to improved survival and health: Modelling 50 years of the Expanded Programme on Immunisation. Lancet. 2024;403(10441):2307-16. https://doi.org/10.1016/S0140-6736(24)00850-X.
2. GBD 2023 Vaccine Coverage Collaborators. Global, regional, and national trends in routine childhood vaccination coverage from 1980 to 2023 with forecasts to 2030: A systematic analysis for the Global Burden of Disease Study 2023. Lancet. 2025;406(10500):235-60. https://doi.org/10.1016/S0140-6736(25)01037-2.
3. Kiang MV, Bubar KM, Maldonado Y, Hotez PJ, Lo NC. Modelling reemergence of vaccine-eliminated infectious diseases under declining vaccination in the US. JAMA. 2025;333(24):2176-87. https://doi.org/10.1001/jama.2025.6495.
4. National Institute for Communicable Diseases. Measles and rubella weekly situation report for South Africa. 2026. Available from: https://www.nicd.ac.za/wp-content/uploads/2026/02/Weekly-measles_outbreak_sitrep_week-6_final.pdf.
5. National Institute for Communicable Diseases. Situational report on toxigenic corynebacterium diphtheriae disease in South Africa, 2024-2026. 2026. Available from: https://www.nicd.ac.za/wp-content/uploads/2026/02/Diphtheria-Situational-Report_week_6_final.pdf.
6. Crichton H, Nkado N, Morrow B, Salie S, Procter C. Critical pertussis infection in the paediatric intensive care unit: A case series in an outbreak. South Afr J Crit Care. 2025;41(1):e2049. https://doi.org/10.7196/SAJCC.2025.v41i1.2049.
7. Thompson S, Meyer JC, Burnett RJ, Campbell SM. Mitigating vaccine hesitancy and building trust to prevent future measles outbreaks in England. Vaccines (Basel). 2023;11(2):288. https://doi.org/10.3390/vaccines11020288.
8. Lazarus JV, White TM, Wyka K, et al. Influence of COVID-19 on trust in routine immunisation, health information sources and pandemic preparedness in 23 countries in 2023. Nat Med. 2024;30(6):1559-63. https://doi.org/10.1038/s41591-024-02939-2.
9. MacDonald NE; SAGE Working Group on Vaccine Hesitancy. Vaccine hesitancy: Definition, scope and determinants. Vaccine. 2015;33(34):4161-4. https://doi.org/10.1016/j.vaccine.2015.04.036.
10. Larson HJ, Gakidou E, Murray CJL. The vaccine-hesitant moment. N Engl J Med. 2022;387(1):58-65. https://doi.org/10.1056/NEJMra2106441.
11. Betsch C, Schmid P, Heinemeier D, et al. Beyond confidence: Development of a measure assessing the 5C psychological antecedents of vaccination. PLoS One. 2018;13(12):e0208601. https://doi.org/10.1371/journal.pone.0208601.
12. Cooper S, Schmidt BM, Sambala EZ, et al. Factors that influence parents' and informal caregivers' views and practices regarding routine childhood vaccination: A qualitative evidence synthesis. Cochrane Database Syst Rev. 2021;10(10):CD013265. https://doi.org/10.1002/14651858.CD013265.pub2.
13. United Nations Children's Fund. The State of the World's Children 2023: For every child, vaccination. Available from: https://www.unicef.org/reports/state-worlds-children-2023#SOWC.
14. Burger R, Köhler T, Golos AM, et al. Longitudinal changes in COVID-19 vaccination intent among South African adults: Evidence from the NIDS-CRAM panel survey, February to May 2021. BMC Public Health. 2022;22(1):422. https://doi.org/10.1186/s12889-022-12826-5.
15. South African Health Products Regulatory Authority. Total doses of COVID-19 vaccines administered to date, including the Sisonke study. Available from: https://aefi-reporting.sahpra.org.za/doses.html.
16. Meyer JC, Al Kaabi N, Abu Hassan MY, et al. Assessing vaccine hesitancy and vaccine literacy in adults in Saudi Arabia, United Arab Emirates, Turkiye and South Africa. Congress of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Global 2025, Vienna, Austria, 11-15 April 2025.
17. Edelman Trust Institute. 2025 Edelman Trust Barometer. Special report: Trust and health in South Africa. Available from: https://www.edelman.com/africa/trust/2025/trust-barometer.
18. Matsangaise MM, Burnett RJ, Ismail Z, Meyer JC. Negative vaccine sentiments on South African social media platforms before the COVID-19 pandemic: A mixed methods study. Front Health Serv. 2025;5:1578992. https://doi.org/10.3389/frhs.2025.1578992.
19. Cooper S, van Rooyen H, Wiysonge CS. COVID-19 vaccine hesitancy in South Africa: How can we maximise uptake of COVID-19 vaccines? Expert Rev Vaccines. 2021;20(8):921-33. https://doi.org/10.1080/14760584.2021.1949291.
20. Opel DJ, Heritage J, Taylor JA, et al. The architecture of provider-parent vaccine discussions at health supervision visits. Paediatrics. 2013;132(6):1037-46. https://doi.org/10.1542/peds.2013-2037.
21. Constable C, Ferguson K, Nicholson J, Quinn GP. Clinician communication strategies associated with increased uptake of the human papillomavirus (HPV) vaccine: A systematic review. CA Cancer J Clin. 2022;72(6):561-9. https://doi.org/10.3322/caac.21753.
22. Fenton AT, Eun TJ, Clark JA, Perkins RB. Indicated or elective? The association of providers'

words with HPV vaccine receipt. Hum Vaccin Immunother. 2018;14(10):2503-9. https://doi.org/10.1080/21645515.2018.1480237.
23. Brown MT, Benson CA. Addressing the challenges of vaccine hesitancy broadly and related to COVID-19 vaccines. Top Antivir Med. 2022;29(5):430-9. PMID: 35191659; PMCID: PMC8862750.
24. Gagneur A, Gutnick D, Berthiaume P, et al. From vaccine hesitancy to vaccine motivation: A motivational interviewing-based approach to vaccine counselling. Hum Vaccin Immunother. 2024;20(1):2391625. https://doi.org/10.1080/21645515.2024.2391625.
25. Nihlén Fahlquist J. Vaccine hesitancy and trust. Ethical aspects of risk communication. Scand J Public Health. 2018;46(2):182-8. https://doi.org/10.1177/1403494817727162.
26. Avelino-Silva VI, Ferreira-Silva SN, Soares MEM, et al. Say it right: Measuring the impact of different communication strategies on the decision to get vaccinated. BMC Public Health. 2023;23(1):1162. https://doi.org/10.1186/s12889-023-16047-2.
27. Freeman D, Loe BS, Yu LM, et al. Effects of different types of written vaccination information on COVID-19 vaccine hesitancy in the UK (OCEANS-III): A single-blind, parallel-group, randomised controlled trial. Lancet Public Health. 2021;6(6):e416-e427. https://doi.org/10.1016/S2468-2667(21)00096-7.
28. Hotez P. It won't end with COVID: Countering the next phase of American antivaccine activism 2025-29. PLOS Glob Public Health. 2025;5(1):e0004020. https://doi.org/10.1371/journal.pgph.0004020.
29. Lewandowsky S, Cook J, Ecker U, et al. The Debunking Handbook 2020. https://doi.org/10.17910/b7.1182.
30. National Institute for Health and Care Research. Promoting vaccination: The right approach for the right group. Public Health 2023. https://doi.org/10.3310/nihrevidence_59296.

The use of creatine in adolescents

C van Staden, M Milne

School of Pharmacy, University of the Western Cape, South Africa
Corresponding author, email: cvanstaden@uwc.ac.za

Abstract

Creatine is a naturally occurring compound essential for cellular energy metabolism and is widely used as a dietary supplement to enhance high-intensity exercise performance. However, its use extends beyond structured athletic performance contexts. Due to broad availability in retail outlets and online platforms, creatine is increasingly used in recreational gym environments, school sports, and by adolescents seeking improvements in physique and muscle mass, often without professional guidance. While creatine supplementation is well established in adults, its use in adolescents remains controversial, largely attributable to ongoing safety concerns, persistent misconceptions, and the limited availability of robust long-term data. Beyond its ergogenic effects, emerging evidence suggests potential for creatine to influence cognitive performance. This review evaluates the prevalence of creatine use in adolescents, its mechanism of action, effects on athletic and cognitive performance, as well as safety profile, with emphasis on the pharmacist's role in counselling and monitoring. Current evidence suggests that creatine supplementation, when used appropriately, is generally well tolerated in adolescents, although long-term safety data remain limited. Pharmacists play a key role in promoting evidence-based use, mitigating risk, addressing misinformation, and supporting safe supplementation practices in adolescent populations.

Keywords: creatine, adolescents, dietary supplements, safety, pharmacist role

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Introduction

Creatine is one of the most extensively researched ergogenic aids in sports nutrition and one of the most widely used dietary supplements worldwide. Synthesised endogenously from arginine, glycine and methionine, and obtained exogenously through dietary sources such as red meat and seafood, creatine plays a central role in cellular energy metabolism. In the skeletal muscles and brain cells, creatine contributes to the phosphocreatine system, which functions as a rapid buffer for adenosine triphosphate (ATP) regeneration during short-duration, high-intensity activity (muscles), and cognitive performance (brain).[1-4]

In adult populations, creatine supplementation has consistently demonstrated improvements in anaerobic performance, lean body mass, and training adaptations, with an established safety profile when used at recommended doses.[2,3] The increasing prevalence of creatine use among adolescent athletes, particularly in strength- and power-based sports, underscores the need for clear, evidence-based guidance.[5-7] Adolescents may initiate supplementation based on peer influence, social media exposure, or performance pressures, frequently without professional supervision. In this context, pharmacists are uniquely positioned to provide structured counselling, evaluate risk factors, and mitigate misinformation.

While the adolescent evidence base is smaller than that of adults, a growing body of controlled trials, observational studies, and clinical investigations has primarily examined performance outcomes, with safety parameters often reported as secondary outcomes in younger populations. These studies generally report modest ergogenic benefits and no consistent signal of clinically significant adverse effects when creatine is used responsibly. Nonetheless, long-term prospective data in healthy adolescent cohorts remain limited, warranting cautious interpretation.[1-3]

For the purposes of this article, adolescence is defined according to the World Health Organization (WHO) as individuals aged 10-19 years.[8] This review evaluates the current literature on creatine use in adolescents, synthesising evidence related to efficacy, safety, and common misconceptions. In addition, it provides practical, pharmacist-focused guidance for assessment, counselling, monitoring, and referral. By distinguishing between documented risks and persistent myths, this article aims to support evidence-informed decision-making in pharmacy settings.

Prevalence of creatine use in adolescents

Creatine supplementation is increasingly used by adolescents, particularly those engaged in competitive or recreational sports for performance enhancement.[9,10] Survey-based studies indicate that prevalence varies by sport type, competitive level, age, and sex.

Across middle- and high-school populations, approximately 5–20% of adolescents report prior or current creatine use.[10] Use is consistently higher among males than females and increases across advancing grade levels.[2,10] For example, Metzl et al.[11] reported use in 8.8% of males and 1.8% of females (Grades 6–12), with 44% of users in Grade 12. Similarly, Hoffman et al.[12] found higher prevalence among males, with rates increasing to 22% in Grade 12 males. Broader estimates suggest the general adolescent population use ranging from 0.6–22.2% in males and 0.6–3% in females.[13]

Among adolescent athletes, similar sex-related trends are observed and prevalence is generally higher, particularly in strength- and power-based sports. McGuine et al.[14] reported use in 16.7% of high school athletes, with the highest rates among football players (30.1%) and the lowest among female cross-country athletes (1.3%). Smith et al.[15] documented an overall prevalence of 8.2% among high school athletes, with rates increasing to 21% among football players. Reported motivations commonly include increasing lean body mass, strength, and anaerobic performance.[2,10] Even higher rates have been observed among adolescents engaging in muscle-building behaviours, particularly older boys and young men.[6]

Among elite adolescent athletes competing internationally, prevalence appears higher than in both school-based and general athletic cohorts. Petroczi et al.[16] reported use in 36.1% of elite adolescent athletes in the United Kingdom, with similar findings in subsequent cohorts (28%).[17] Jovanov et al.[18] reported use in 25.3% of internationally competing adolescent athletes across four countries, with higher use among males and older adolescents. Although earlier school-based studies suggested very low use among females, more recent elite cohorts demonstrate greater female representation among users.[18,19]

Despite these findings, creatine remains less frequently used than other dietary supplements such as protein powders and multivitamins which may reach prevalence rates of 60–80% in athletic populations.[2] Overall, evidence indicates higher use among males, older adolescents, and those participating in strength-oriented and elite sport, reflecting the growing normalisation of creatine supplementation in adolescent athletic contexts.

Mechanism of action of creatine

The mechanism of action of creatine is the same across age groups, with similar phosphocreatine-mediated ATP buffering system working in both adolescents and adults. Creatine exerts its primary physiological effect through augmentation of the intramuscular phosphocreatine system, a critical component of short-duration, high-intensity energy metabolism. Approximately 95% of total body creatine is stored in skeletal muscle, where it exists as free creatine and phosphocreatine.[2,20-22]

Creatine is derived from two principal sources (Figure 1). It is synthesised endogenously, from dietary sources such as red meat and fish, through a two-step process. Initially, arginine and glycine are converted to guanidinoacetate (GAA) in the kidneys via arginine:glycine amidinotransferase (AGAT). GAA is then methylated in the liver by S-adenosylmethionine (SAM), which serves as the methyl donor, to produce creatine; this reaction generates S-adenosylhomocysteines (SAH) as a by-product. Once transported to target tissues such as skeletal muscle, creatine is phosphorylated to phosphocreatine, which acts as a rapid energy buffer by donating inorganic phosphate (Pi) to adenosine diphosphate (ADP) to regenerate ATP (Figure A.1).[20-22]

Although the majority of creatine is endogenously synthesised in the kidneys and liver, a small amount is also synthesised in the brain. This occurs through enzymatic catalysation of arginine, glycine, and methionine to supply 20% of the body's energy expenditure.[4] This involves a two-step process. Firstly, AGAT synthesises GAA from arginine and glycine. Secondly GAMT (guanidinoacetate N-methyltransferase) methylates GAA to produce creatine, using S-adenosyl-L-methionine (SAMe). Creatine is then transported from the extracellular space into the cells through the sodium-chloride dependent transporter, Solute Carrier Family 6 Member 8 (SLC6A8), against a concentration gradient (Figure A.2).[23]

In addition to endogenous synthesis, creatine is obtained exogenously through creatine supplementation (Figure 1B).[20-22] Following absorption in the small intestine, supplemental creatine enters the systemic circulation and is transported into skeletal muscle through the sodium-dependent creatine transporter (CRT-1). Within the muscle cell, creatine is phosphorylated by creatine kinase (CK) using ATP generated through mitochondrial oxidative phosphorylation. During short-duration, high-intensity exercise, ATP is rapidly hydrolysed to adenosine ADP to supply energy for muscle contraction. This reversible reaction enables phosphocreatine to function as an immediate phosphate donor during periods of high ATP demand, thereby maintaining intracellular ATP concentrations and sustaining muscle contractile function.[1-3,20,22] The CK reaction, shown below (Equation 1), regenerates ATP from ADP:

Creatine + ATP ⇌ phosphocreatine + ADP …(Equation 1)

Creatine supplementation increases total intramuscular creatine and phosphocreatine concentrations, thereby enhancing rapid ATP buffering capacity. Following optional loading protocols, a typical maintenance dose of 3–5 g/day is sufficient to sustain elevated intramuscular creatine stores in most individuals. Increased phosphocreatine availability support improvements in repeated sprint performance, peak power output, and resistance training adaptations in adolescent populations.[1-3]

In addition to its energetic role, intracellular creatine accumulation exerts osmotic effects, increasing intracellular osmolarity and promoting water influx into muscle cells (Figure 1). This cellular hydration may reduce protein breakdown, enhance anabolic signalling, and improve recovery following resistance training through the activation of the mTOR (mechanistic Target of Rapamycin)-related pathways.[1-3]

Effects on athletic performance in adolescents

The evidence evaluating the ergogenic effects of creatine supplementation in adolescent populations is evolving but remains less robust than that in adults. A 2023 systematic review of creatine use in paediatric and adolescent athletes identified 13 eligible studies involving participants aged approximately 11.5–18.2 years.[5] Although many of these studies were randomised controlled trials, the review concluded that the overall methodological quality was low and that findings regarding

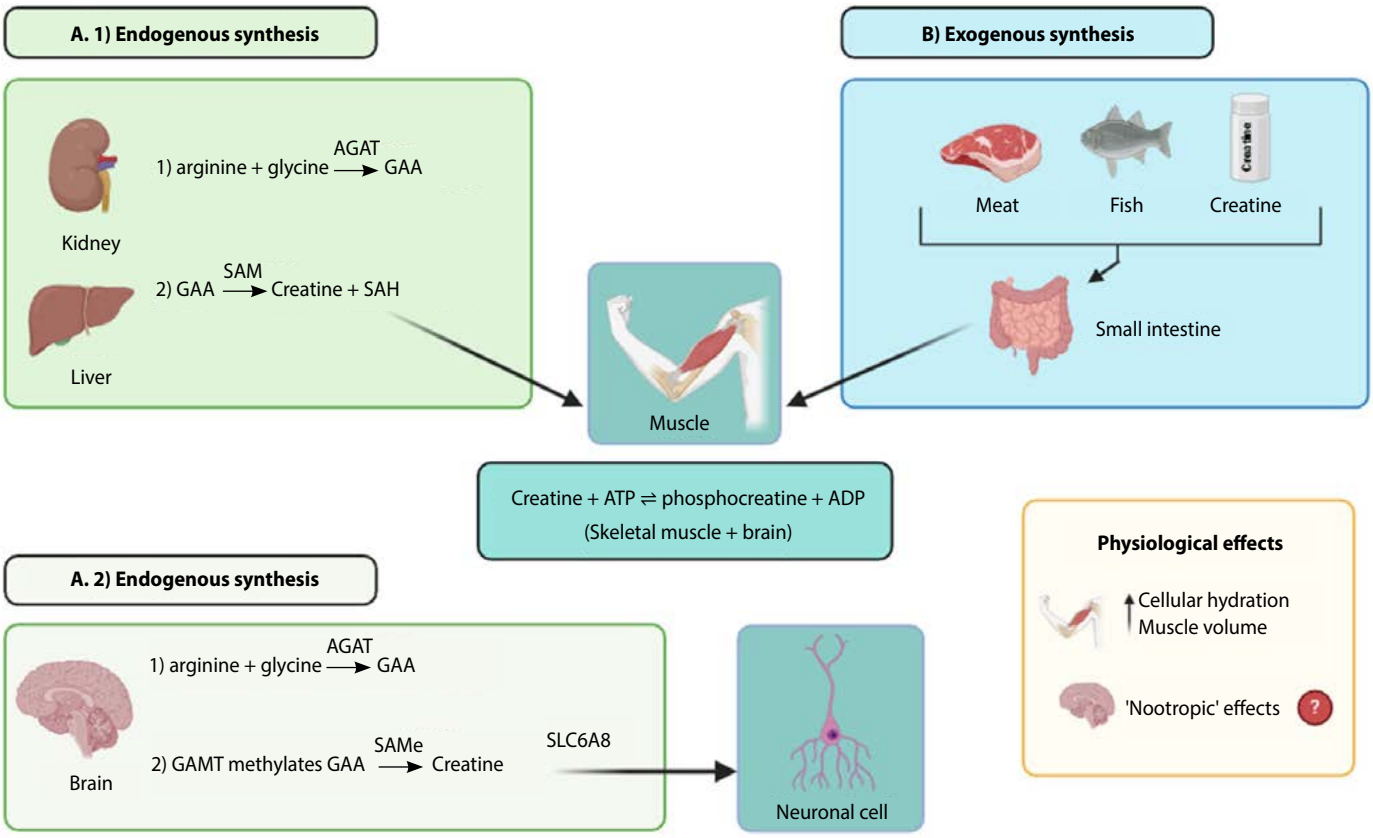

Figure 1: Synthesis and mechanism of action of creatine supplementation in skeletal muscle and the brain with associated physiological effects. Schematic illustration created by the authors based on published descriptions of creatine absorption, synthesis, transport, phosphocreatine buffering, CK shuttle activity, intracellular hydration effects, and anabolic signalling mechanisms.[1-3]

Abbreviations: ATP – adenosine triphosphate, ADP – adenosine diphosphate, GAA – guanidinoacetate, AGAT – arginine:glycine amidinotransferase, SAM – S-adenosylmethionine, SAMe – S-adenosyl-L-methionine, SAH – S-adenosylhomocysteines, Pi – inorganic phosphate, SLC6A8 – Solute Carrier Family 6 Member 8, CK – creatine kinase. Created with BioRender.com.

performance outcomes were inconsistent. Most studies focused on soccer and swimming cohorts, and heterogeneity in dosing protocols, supplementation duration, and outcome measures limited comparability. The authors concluded that, while some performance improvements were observed, definitive conclusions regarding efficacy in adolescents cannot yet be made due to study limitations.

Similarly, Jagim et al.[2] reviewed creatine supplementation in children and adolescents and reported that several studies demonstrate improvements in strength, sprint performance, and high-intensity exercise capacity. Importantly, this review noted limited evidence of ergolytic effects and suggested that creatine's physiological rationale in adolescents is comparable to that observed in adults, given its role in phosphocreatine resynthesis and rapid ATP regeneration. However, the authors also emphasised that the volume of high-quality paediatric and adolescent data remains small relative to adult literature.

More recent literature suggests that performance benefits may be more context specific. A 2024 review by Ortiz-Barroso et al.[24] reported positive effects on muscular function and physical performance in adolescent athletes but highlighted substantial variability in dosing regimens and study design. This heterogeneity complicates the ability to establish standardised recommendations, particularly in younger populations where maturation status may influence responsiveness.

Notably, newer controlled trials provide stronger sport-specific evidence. In a 2024 double-blind, placebo-controlled study in adolescent soccer players (~17 years), Huerta Ojeda et al.[25] demonstrated that low-dose creatine supplementation (0.3 g/kg/day for 14 days) improved muscle power output following acute fatigue compared to placebo. This finding is clinically meaningful, as fatigue resistance and recovery capacity are highly relevant to competitive match conditions.

Extending beyond pure strength outcomes, a 2025 randomised crossover trial in adolescent basketball players (13–14 years) found that acute creatine supplementation enhanced technical performance during cognitively demanding dual-task conditions and reduced internal load.[26] These findings suggest that creatine may influence not only muscular power but also performance during complex motor-cognitive integration tasks, which are central to many team sports.

Collectively, current evidence indicates that creatine supplementation may improve muscular power, repeated sprint ability, fatigue resistance, and potentially sport-specific technical performance in adolescents. However, the literature remains

characterised by small sample sizes, protocol heterogeneity, and limited long-term follow-up. While emerging data are promising, adequately powered studies are required before definitive performance claims can be established for adolescent populations.

Effects on cognitive function in adolescents

The term 'nootropics' is commonly used to describe compounds proposed to enhance cognitive function.[27] Creatine has been investigated for its potential 'nootropic' effects, with some studies reporting improvements in specific cognitive domains, including attention, memory, and executive function, whereas others have failed to demonstrate significant cognitive benefit.[27-29] Notably, most of this research has been conducted in the adult population, with comparatively limited data specifically evaluating adolescents.[28,29]

Findings from early controlled trials are conflicting. Some investigations report improvements in tasks involving short-term memory, reasoning, or rapid information processing, while others demonstrate no measurable benefit.[29] Differences in dietary intake may further influence response, particularly among individuals with lower baseline creatine stores, such as vegetarians. For example, Benton et al.[30] observed improvements in short-term memory among vegetarians but not meat-eaters. In contrast, Sandkühler et al.[31] reported only modest effects, with no additional cognitive benefit observed in vegetarians compared with omnivores.

Some evidence suggests that cognitive effects may be more apparent under conditions of physiological stress, such as sleep deprivation or mental fatigue. Gordji-Nejad et al.[32] reported improved cognitive performance following a single high dose of creatine in sleep-deprived individuals, and sleep-deprived rugby players demonstrated improved throwing accuracy after supplementation.[33] However, these findings are not consistently supported, and some reviews conclude that overall evidence for cognitive benefit remains inconclusive.[28]

Evidence specific to adolescents remain limited. In a study examining both brain creatine concentrations and cognitive performance in adolescents, no significant changes were observed in either outcome following supplementation.[34] These findings highlight the difficulty of extrapolating adult data to younger populations.

Overall, the current literature on cognitive effects is derived largely from adult studies and is limited by small sample sizes, short supplementation durations, variable dosing protocols, and heterogeneous cognitive outcome measures. Differences in baseline dietary creatine intake, age ranges, and methodological design further complicate interpretation. Given the paucity of adolescent-specific data and the inconsistency of adult findings, well-designed, adequately powered trials in adolescents are required before definitive conclusions can be drawn. Nonetheless, this remains an emerging and evolving area of research.

Safety considerations

With the increasing use of creatine among adolescents, its safety in this population warrants consideration. Although creatine is well-established as safe and well tolerated in adults across short- and long-term studies,[1,35,36] comparatively limited research has evaluated its safety in adolescents.

A review by Jagim et al.[2] reported no evidence of adverse effects in adolescent athletic populations. However, the included studies were generally small, short in duration, and primarily assessed performance rather than comprehensive clinical safety markers. While short-term use appeared well tolerated, long-term clinical safety remains insufficiently characterised.

Renal safety

Renal safety remains one of the most frequently discussed concerns.[3,5] However, current evidence does not support an association between creatine supplementation and kidney injury in healthy individuals, including adolescents and young adults.[37] Although modest increases in serum creatinine may occur, these do not reflect renal dysfunction.[37,38]

Growth and musculoskeletal development

Concerns have also been raised regarding supplementation during periods of rapid growth and musculoskeletal development.[5,39] As an osmotically active compound, creatine increases intramuscular water content and total body mass, contributing to gains in lean mass and strength.[5] However, the long-term implications during pubertal development and potential effects on musculoskeletal maturation remain insufficiently studied.[40,41]

Hydration and thermoregulation

Related concerns include dehydration and muscle cramping, as creatine's effects on intracellular water distribution have been speculated to impair thermoregulation during intense exercise, extreme heat, or fluid loss.[3] However, adult data do not demonstrate an increased risk of dehydration or heat-related illness at recommended dosages,[42] and similar findings have been reported in adolescent football players.[43] Some evidence further suggests that creatine's osmotic effects may attenuate exercise-induced increases in core body temperature and heart rate, potentially mitigating heat-related risk.[3,42]

Clinical, regulatory and additional health-related concerns

Evidence from younger populations further supports the tolerability of creatine supplementation. In children, creatine has been associated with clinical and functional improvements in conditions including systemic lupus erythematosus and neuromuscular conditions, without adverse effects on laboratory markers such as renal function.[44,45] Improved outcomes following traumatic brain injury have similarly been reported in children and adolescents receiving supplementation.[46]

Table I: Pre-supplementation assessment checklist for creatine use in adolescents

Domain	Key considerations	Reference
Age and supervision	Adolescence defined as 10-19 years (WHO); parental awareness is recommended	2, 5, 8
Indication	Most evidence in high-intensity, repeated effort sports	2, 25
Medical history	Screen for underlying renal disease or relevant risk factors	2, 5
Concurrent medications	Assess use of nephrotoxic medications or agents affecting renal haemodynamics	5
Dietary intake	Vegetarian diets may be associated with lower baseline creatine stores	2
Training load	Structured and consistent training is required to drive benefit	2, 5

Table II: Medicines and supplement combinations requiring caution with creatine supplementation

Category	Examples	Clinical concern	Reference
Nephrotoxic medications	Chronic non-steroidal anti-inflammatory drugs (NSAIDs); aminoglycosides; high-dose antivirals	Potential additive renal stress in individuals with pre-existing risk factors	2, 5
Agents affecting renal perfusion	Angiotensin-converting enzyme (ACE) inhibitors; angiotensin II receptor blockers (ARBs)	Altered renal haemodynamics may complicate renal monitoring in higher-risk individuals	5
Stimulant-containing supplements	High-caffeine pre-workout products; sympathomimetic agents	Increased risk of dehydration and heat-related complications during intense training	2
Excessive protein stacking	High-dose protein supplementation combined with creatine	May affect hydration balance and increase gastrointestinal discomfort	2

Regulatory assessments further support the safety profile of creatine. The United States Food and Drug Administration (FDA) classify creatine as Generally Recognized as Safe (GRAS) for its intended use, reflecting expert consensus that available evidence supports its safety under specified conditions, including in older children and adolescent populations.[1]

Available evidence does not demonstrate a direct association between creatine supplementation and eating disorders, and no adverse effects have been identified in individuals with psychiatric conditions.[47] A recent prospective study reported an association with muscle dysmorphia symptomatology in adolescents and young adults.[48] However, these findings are limited due to reliance on self-reported data and non-probability sampling.

Finally, Simpson et al.[49] observed a trend towards increased markers of airway inflammation and responsiveness in adolescent elite soccer players following creatine supplementation, suggesting a potential adverse effect on airway function. As this finding is limited to a single investigation, further research is required before definitive conclusions can be drawn.

Overall, although adolescent-specific evidence is limited, current data suggest that creatine supplementation is generally safe and well tolerated when used appropriately. Further high-quality, long-term studies are needed to better define its safety profile in this population.

Pharmacist counselling and monitoring considerations

Pharmacists are frequently consulted regarding creatine supplementation and are well positioned to provide evidence-based guidance. In adolescent populations as previously stated 10–19 years), pharmacists play a critical role in structured assessment, appropriate counselling, product selection, monitoring, and referral where necessary.[2,5] Creatine use in this age group should not be casual or unsupervised. Assessment must precede recommendation.[2,5]

Structured assessment framework

Creatine supplementation is most evidence-based in activities requiring short-duration, high-intensity, repeated efforts including sprinting, resistance training, and soccer.[2,25] It has limited relevance in endurance-only sports including triathlon (Ironman) marathon, ultra-marathon, and mountain biking.[2] Moreover, adolescents should be engaged in structured, progressive training before supplementation is considered.[2,5] Table I outlines a practical checklist to guide pharmacists during counselling.

Medication and supplement interaction screening

Although direct pharmacokinetic drug-creatine interactions are uncommon, the potential cumulative renal load should be considered.[2,5] Adolescents with pre-existing renal disease or identifiable risk factors should be referred for medical evaluation prior to initiating supplementation.[5] In addition to Table I, Table II provides a practical cross-reference tool to support screening for medicine and supplement combinations requiring caution with creatine.

Dietary considerations

Baseline dietary creatine intake influences response to supplementation. Individuals consuming low meat or vegetarian diets may have lower intramuscular creatine stores and demonstrate greater responsiveness to supplementation.[2] However, supplementation does not compensate for inadequate caloric or protein intake. Creatine is most beneficial when combined with structured resistance training and adequate nutrition.[2,5]

Counselling messages for adolescents and parents/guardians

Pharmacists should emphasise that creatine supplementation supports an endogenous energy system.[2] Benefits are most evident in short-duration, high-intensity activities.[2,25] Importantly, creatine does not replace training or proper nutritional practices,[5] and it should not be viewed as a rapid cosmetic intervention. Typical dosing strategies include an optional loading phase followed by a maintenance dose of 3–5 g/day to maintain elevated intramuscular stores.[2] Consistency in training and dosing is more important than aggressive supplementation strategies.[2]

Product selection

Creatine monohydrate remains the most extensively studied and evidence-supported form.[2] Pharmacists should recommend single-ingredient creatine monohydrate products that have undergone quality testing to ensure purity and avoid proprietary blends. Gastrointestinal discomfort may occur in some individuals. However, this can be minimised by dividing the daily dose and consuming it with meals.[2]

Monitoring during use and referral

Monitoring of adolescent creatine users should include periodic review of gastrointestinal symptoms, evaluation of dosing adherence and duration of use, and confirmation that supplementation aligns with structured training practices. Reassessment every 3–6 months is advisable in this population.[2,5] Referral should be considered if renal symptoms develop, if inappropriate supplement stacking or excessive stimulant use is identified, or if underlying medical risk factors are present. Referral is also recommended for adolescents with pre-existing renal disease or concerning supplement-use behaviours.

Conclusion

In conclusion, creatine use among adolescents is increasing, particularly among males and in elite or strength-oriented sporting contexts. Current evidence suggests that creatine supplementation may improve muscular power and fatigue resistance and is generally well tolerated when used appropriately. However, evidence supporting its use for cognitive enhancement remains limited. Although adolescent-specific data remain minimal, available studies do not indicate significant safety concerns. Long-term, high-quality, and adequately powered trials are needed to support safety and efficacy in both athletic and non-athletic adolescent populations. Similar requirements are needed for the evaluation of cognitive outcome. Until such data are available, access to accurate, evidence-based information remains essential, with pharmacists playing a central role in counselling, risk assessment, and guiding safe supplementation practices.

Conflict of interest

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ORCID

C van Staden https://orcid.org/0000-0002-0080-0230

M Milne https://orcid.org/0000-0002-9982-029X

References

1. Kreider RB, Jagim AR, Antonio J, et al. Creatine supplementation is safe, beneficial throughout the lifespan, and should not be restricted. Front Nutr. 2025;12:1578564. https://doi.org/10.3389/fnut.2025.1578564.
2. Jagim AR, Kerksick CM. Creatine supplementation in children and adolescents. Nutrients. 2021;13(2):664. https://doi.org/10.3390/nu13020664.
3. Antonio J, Candow DG, Forbes SC, et al. Common questions and misconceptions about creatine supplementation: What does the scientific evidence really show? J Int Soc Sports Nutr. 2021;18(1):13. https://doi.org/10.1186/s12970-021-00412-w.
4. Candow DG, Forbes SC, Ostojic SM, et al. "Heads up" for creatine supplementation and its potential applications for brain health and function. Sports Med. 2023 Dec;53(Suppl 1):49-65. https://doi.org/10.1007/s40279-023-01870-9. Epub 2023 Jun 27. Erratum in: Sports Med. 2024;54(1):235-236. https://doi.org/10.1007/s40279-023-01888-z.
5. Metzger GA, Minneci PM, Gehred A, Day A, Klingele KE. Creatine supplementation in the pediatric and adolescent athlete: A literature review. J Orthop. 2023;38:73-8. https://doi.org/10.1016/j.jor.2023.03.010.
6. Ganson KT, Nagata JM. Adolescent and young adult use of muscle-building dietary supplements: Guidance for assessment and harm reduction approaches to mitigate risks. J Adolesc Health. 2024 Sep;75(3):379-82. https://doi.org/10.1016/j.jadohealth.2024.05.027.
7. Vargas-Molina S, García-Sillero M, Kreider RB, et al. A randomised open-labeled study to examine the effects of creatine monohydrate and combined training on jump and scoring performance in young basketball players. J Int Soc Sports Nutr. 2022;19(1):529-42. https://doi.org/10.1080/15502783.2022.2108683.
8. World Health Organization. Adolescent health. Geneva: World Health Organization. Available from: https://www.who.int/health-topics/adolescent-health. Accessed February 2026.
9. Knapik JJ, Steelman RA, Hoedebecke SS, et al. Prevalence of dietary supplement use by athletes: Systematic review and meta-analysis. Sports Med. 2016;46(1):103-23. https://doi.org/10.1007/s40279-015-0387-7.
10. Jagim AR, Stecker RA, Harty PS, Erickson JL, Kerksick CM. Safety of creatine supplementation in active adolescents and youth: A brief review. Front Nutr. 2018;5:427078. https://doi.org/10.3389/fnut.2018.00115.
11. Metzl JD, Small E, Levine SR, Gershel JC. Creatine use among young athletes. Pediatrics. 2001;108(2):421-5. https://doi.org/10.1542/peds.108.2.421.
12. Hoffman JR, Faigenbaum AD, Ratamess NA, et al. Nutritional supplementation and anabolic steroid use in adolescents. Med Sci Sports Exerc. 2008;40(1):15-24. https://doi.org/10.1249/mss.0b013e31815a5181.
13. Svantorp-Tveiten KME, Friborg O, Torstveit MK, et al. Protein, creatine, and dieting supplements among adolescents: Use and associations with eating disorder risk factors, exercise-, and sports participation, and immigrant status. Front Sports Act Living. 2021;3:727372. https://doi.org/10.3389/fspor.2021.727372.
14. McGuine TA, Sullivan JC, Bernhardt DA. Creatine supplementation in Wisconsin high school athletes. WMJ. 2002;101(2):25-30. PMID: 12085493.
15. Smith J, Dahm DL, editors. Creatine use among a select population of high school athletes. Mayo Clinic Proceedings. 2000;75(12):1257-63. https://doi.org/10.4065/75.12.1257.
16. Petróczi A, Naughton DP, Mazanov J, Holloway A, Bingham J. Performance enhancement with supplements: Incongruence between rationale and practice. J Int Soc Sports Nutr. 2007;4:19. https://doi.org/10.1186/1550-2783-4-19.
17. Petroczi A, Naughton DP. The age-gender-status profile of high performing athletes in the UK taking nutritional supplements: Lessons for the future. J Int Soc Sports Nutr. 2008;5(1):2. https://doi.org/10.1186/1550-2783-5-2.
18. Jovanov P, Đorđić V, Obradović B, et al. Prevalence, knowledge and attitudes towards using sports supplements among young athletes. J Int Soc Sports Nutr. 2019;16(1):27. https://doi.org/10.1186/s12970-019-0294-7.
19. Ray TR, Eck JC, Covington LA, et al. Use of oral creatine as an ergogenic aid for increased sports performance: Perceptions of adolescent athletes. South Med J. 2001;94(6):608-12. https://doi.org/10.1097/00007611-200106000-00014.
20. Wallimann T, Wyss M, Brdiczka D, Nicolay K, Eppenberger H. Intracellular compartmentation, structure and function of creatine kinase isoenzymes in tissues with high and fluctuating energy demands: The 'phosphocreatine circuit' for cellular energy homeostasis. Biochem J. 1992;281 (Pt 1)(Pt 1):21-40. https://doi.org/10.1042/bj2810021.
21. Wyss M, Kaddurah-Daouk R. Creatine and creatinine metabolism. Physiological reviews. 2000;80(3):1107-213. https://doi.org/10.1152/physrev.2000.80.3.1107.
22. Buford TW, Kreider RB, Stout JR, et al. International Society of Sports Nutrition position

stand: Creatine supplementation and exercise. J Int Soc Sports Nutr. 2007;4:6. https://doi.org/10.1186/1550-2783-4-6.
23. Ribeiro F, Forbes SC, Candow DG, et al. Creatine supplementation and muscle-brain axis: A new possible mechanism? Front Nutr. 2025;12:1579204. https://doi.org/10.3389/fnut.2025.1579204.
24. Ortiz-Barroso GS, Espinoza-López F, Ocón-García SG, Salazar-Ramos RM, Esparza-Villalpando V. Effect of creatine supplementation on muscular function and physical performance in children and adolescents a literature review. Arch Latinoam Nutr. 2024;74(3):222-39. https://doi.org/10.37527/2024.74.3.007.
25. Huerta Ojeda Á, Jofré-Saldía E, Torres-Banduc M, et al. Effects of a low dose of orally administered creatine monohydrate on post-fatigue muscle power in young soccer players. Nutrients. 2024 Apr 28;16(9):1324. https://doi.org/10.3390/nu16091324. PMID: 38732571; PMCID: PMC11085131. https://doi.org/10.3390/nu16091324
26. Wu J, Qiu P, Li Y. Acute creatine supplementation enhances technical performance in adolescent basketball players under cognitive-motor dual-task condition. J Int Soc Sports Nutr. 2025;22(sup1):2542369. https://doi.org/10.1080/15502783.2025.2542369.
27. Pastina JT, Stewart LK. Nootropic supplements and exercise: Patterns and perceptions of cognitive enhancer use in physically active individuals. J Diet Suppl. 2026;23(1):23-41. https://doi.org/10.1080/19390211.2025.2589784.
28. Dolan E, Gualano B, Rawson ES. Beyond muscle: The effects of creatine supplementation on brain creatine, cognitive processing, and traumatic brain injury. Eur J Sport Sci. 2019;19(1):1-14. https://doi.org/10.1080/17461391.2018.1500644.
29. Avgerinos KI, Spyrou N, Bougioukas KI, Kapogiannis D. Effects of creatine supplementation on cognitive function of healthy individuals: A systematic review of randomized controlled trials. Exp Gerontol. 2018;108:166-73. https://doi.org/10.1016/j.exger.2018.04.013.
30. Benton D, Donohoe R. The influence of creatine supplementation on the cognitive functioning of vegetarians and omnivores. Br J Nutr. 2011;105(7):1100-5. https://doi.org/10.1017/S0007114510004733.
31. Sandkühler JF, Kersting X, Faust A, et al. The effects of creatine supplementation on cognitive performance: A randomised controlled study. BMC Med. 2023;21(1):440. https://doi.org/10.1186/s12916-023-03146-5.
32. Gordji-Nejad A, Matusch A, Kleedörfer S, et al. Single dose creatine improves cognitive performance and induces changes in cerebral high energy phosphates during sleep deprivation. Sci Rep. 2024;14(1):4937. https://doi.org/10.1038/s41598-024-54249-9.
33. Cook CJ, Crewther BT, Kilduff LP, Drawer S, Gaviglio CM. Skill execution and sleep deprivation: Effects of acute caffeine or creatine supplementation-a randomized placebo-controlled trial. J Int Soc Sports Nutr. 2011;8:2. https://doi.org/10.1186/1550-2783-8-2.
34. Merege-Filho CAA, Otaduy MCG, de Sá-Pinto AL, et al. Does brain creatine content rely on exogenous creatine in healthy youth? A proof-of-principle study. Appl Physiol Nutr Metab. 2017;42(2):128-34. https://doi.org/10.1139/apnm-2016-0406.
35. Balestrino M, Adriano E. Beyond sports: Efficacy and safety of creatine supplementation in pathological or paraphysiological conditions of brain and muscle. Med Res Rev. 2019;39(6):2427-59. https://doi.org/10.1002/med.21590.
36. Gualano B, Rawson ES, Candow DG, Chilibeck PD. Creatine supplementation in the aging population: Effects on skeletal muscle, bone and brain. Amino acids. 2016;48(8):1793-805. https://doi.org/10.1007/s00726-016-2239-7.
37. De Souza e Silva A, Pertille A, Barbosa CGR, et al. Effects of creatine supplementation on renal function: A systematic review and meta-analysis. J Ren Nutr. 2019;29(6):480-9. https://doi.org/10.1053/j.jrn.2019.05.004.
38. Poortmans JR, Francaux M. Adverse effects of creatine supplementation: Fact or fiction? Sports Med. 2000;30(3):155-70. https://doi.org/10.2165/00007256-200030030-00002.
39. Grimby G, Saltin B. The ageing muscle. Clin Physiol. 1983;3(3):209-18. https://doi.org/10.1111/j.1475-097X.1983.tb00704.x.
40. Minahan CL, Poke DP, Morrison J, Bellinger PM. Muscle damage and metabolic responses to repeated-sprint running with and without deceleration. J Strength Cond Res. 2020;34(12):3423-30. https://doi.org/10.1519/JSC.0000000000002164.
41. Manojlović V, Erčulj F. Using blood lactate concentration to predict muscle damage and jump performance response to maximal stretch-shortening cycle exercise. J Sports Med Phys Fitness. 2019;59(4):581-6. https://doi.org/10.23736/S0022-4707.18.08346-9.
42. Sobolewski EJ, Thompson BJ, Smith AE, Ryan ED. The physiological effects of creatine supplementation on hydration: A review. Am J Lifestyle Med. 2011;5(4):320-7. https://doi.org/10.1177/1559827611406071.
43. Greenwood M, Kreider RB, Melton C, et al. Creatine supplementation during college football training does not increase the incidence of cramping or injury. Mol Cell Biochem. 2003;244(1-2):83-8. https://doi.org/10.1023/A:1022413202549.
44. Hayashi A, Solis M, Sapienza M, et al. Efficacy and safety of creatine supplementation in childhood-onset systemic lupus erythematosus: A randomized, double-blind, placebo-controlled, crossover trial. Lupus. 2014;23(14):1500-11. https://doi.org/10.1177/0961203314546017.
45. Tarnopolsky M, Mahoney D, Vajsar J, et al. Creatine monohydrate enhances strength and body composition in Duchenne muscular dystrophy. Neurology. 2004;62(10):1771-7. https://doi.org/10.1212/01.WNL.0000125178.18862.9D.
46. Sakellaris G, Kotsiou M, Tamiolaki M, et al. Prevention of complications related to traumatic brain injury in children and adolescents with creatine administration: An open label randomised pilot study. J Trauma. 2006;61(2):322-9. https://doi.org/10.1097/01.ta.0000230269.46108.d5.
47. Hewlings SJ. Eating disorders and dietary supplements: A review of the science. Nutrients. 2023;15(9):2076. https://doi.org/10.3390/nu15092076.
48. Ganson KT, Testa A, Nagata JM. Creatine monohydrate use is prospectively associated with muscle dysmorphia symptomatology. Eat Behav. 2024;54:101910. https://doi.org/10.1016/j.eatbeh.2024.101910.
49. Simpson AJ, Horne S, Sharp P, Sharps R, Kippelen P. Effect of creatine supplementation on the airways of youth elite soccer players. Med Sci Sports Exerc. 2019;51(8):1582-90. https://doi.org/10.1249/MSS.0000000000001979.

Lenacapavir in HIV prevention care: What the pharmacist should know

KP Selomo, NM Moloto, MJ Luvhimbi, E Bronkhorst

Department of Clinical Pharmacy, Sefako Makgatho Health Sciences University, South Africa

Corresponding author, email: elmien.bronkhorst@smu.ac.za

Abstract

Despite advances in antiretroviral therapy, multidrug-resistant human immunodeficiency virus (HIV) remains a major challenge. Novel agents with unique mechanisms of action and long-acting formulations are needed to improve treatment outcomes, adherence, and patient support. Lenacapavir is the first agent in the class HIV-capsid inhibitors. It disrupts multiple stages of viral replication, including capsid disassembly, nuclear import, and virion maturation. Its administration by long-acting subcutaneous formulation enables dosing every six months, addressing non-compliance associated with daily oral therapy. Lenacapavir shows potent antiviral activity against both treatment-naïve and multidrug-resistant HIV-1 strains. Lenacapavir is a potentially transformative HIV prevention tool, indicated in pre-exposure prophylaxis. Pharmacists play a crucial role in optimising therapy by providing patient education, monitoring adherence, managing drug–drug interactions, and supporting both treatment and preventative strategies, including potential long-acting pre-exposure prophylaxis. Overall, lenacapavir provides a promising and practical alternative that could improve patient outcomes, reduce new infections through effective pre-exposure prophylaxis and strengthen ongoing efforts to control the HIV epidemic.

Keywords: lenacapavir, capsid inhibitor, long-acting ART, HIV, pre-exposure prophylaxis

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Introduction

Human immunodeficiency virus (HIV) remains a significant global health burden despite advances in antiretroviral therapy (ART). The widespread use of potent agents, particularly integrase strand transfer inhibitors, has improved viral suppression rates, reduced HIV-related morbidity and mortality and rendered the disease a manageable chronic condition.[1,2] While ART has revolutionised HIV care, the requirement for daily, lifelong adherence causes treatment fatigue, leading to missed doses, potential virologic failure, and the development of drug-resistant strains.[3,4] Even with great successes of ART, the new HIV infection rates recorded in South Africa in 2024 were more than 170 000. This figure reflects the need for improved efforts in prevention of transmission of the virus.[5]

The development of long-acting ART is transforming HIV care by addressing the limitations of older ART regimens, such as a variety of side-effects and the lack of adherence to treatment regimens.[6] Lenacapavir (GS-6207) is a first-in-class capsid inhibitor that disrupts multiple stages of the HIV replication cycle, offering activity against multidrug-resistant HIV-1.[7] This is a long-acting formulation administered subcutaneously every six months, presents a promising approach to overcoming adherence barriers associated with daily regimens and high pill-burden.[8,9]

Beyond its role in HIV treatment, lenacapavir has emerged as a groundbreaking agent for HIV prevention, particularly in the context of pre-exposure prophylaxis (PrEP) where infrequent dosing could improve uptake and adherence.[9,10] Lenacapavir was registered in October 2025 by the South African Health Products Regulatory Authority (SAHPRA) and roll-out for the PrEP starts in April 2026.[11] This review provides an overview of lenacapavir, focusing on its mechanism of action, safety profile, and the role of a pharmacist in its use.

Mechanism of action

Lenacapavir exerts its antiviral activity by selectively targeting the HIV-1 capsid protein (p24), a structural component essential for multiple stages of the viral replication cycle. It binds to a highly conserved interface between capsid subunits within the hexameric lattice, thereby altering capsid stability and function.[12,13] In the early stages of infection, lenacapavir interferes with essential capsid-dependent processes such as uncoating and interactions with host nuclear transport proteins, including CPSF6 and nucleoporins. This interference prevents the efficient transport of viral DNA into the nucleus, subsequently inhibiting integration into the host genome.[14]

In addition to its early-stage effects, lenacapavir also inhibits the late stage of viral replication by impairing capsid assembly and maturation. It induces abnormal stabilisation of the capsid lattice, a process often described as "hyperstabilisation," which disrupts the normal balance between capsid hexamer and pentamer formation. This leads to the production of structurally defective and non-infectious virions.[15] Furthermore, lenacapavir does not inhibit proteolytic cleavage of Gag; instead, it alters the structural organisation of the capsid during virion maturation, resulting in impaired infectivity of newly formed viral particles.[16]

By targeting a structural protein rather than a viral enzyme, lenacapavir uniquely exerts its effects across multiple stages of the

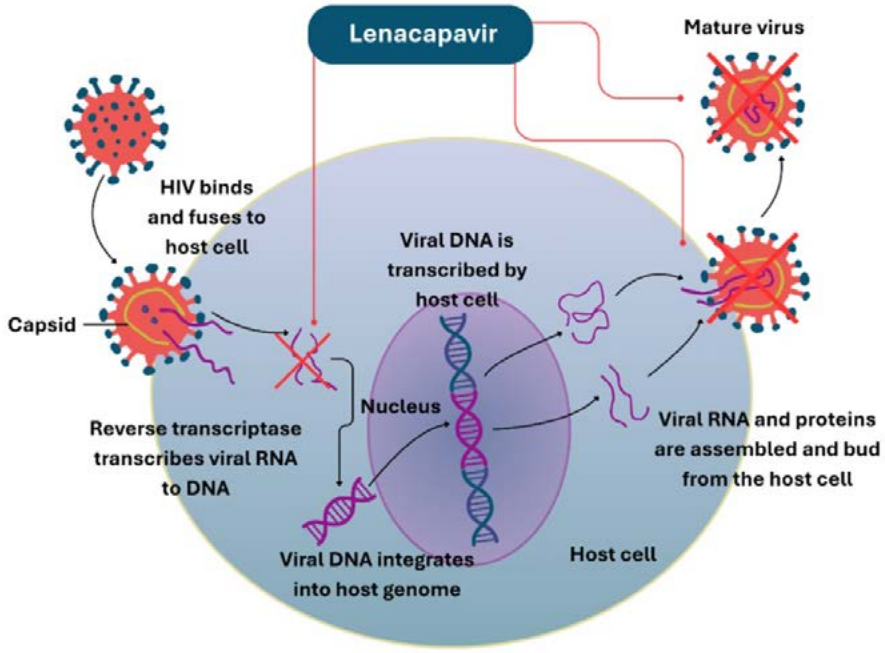

Figure 1: *Multistep inhibition of the HIV life cycle.

*Lenacapavir inhibits HIV by: 1) Target HIV-1 capsid protein, 2) inhibit late-stage replication by impairing capsid assembly, 3) alter structural organisation of capsid during virion maturation
Indication for the use of lenacapavir in South Africa

HIV lifecycle, including nuclear entry, capsid assembly, and virion maturation, preventing viral replication by inhibiting the proper assembly and function of the viral core. This multistage mechanism contributes to its potent antiviral activity and effectiveness against strains of HIV that are resistant to other classes of antiretroviral drugs.[14,17] Figure 1 shows the mechanism of action of lenacapavir inhibiting multiple stages of the HIV life cycle.

Lenacapavir is indicated for the treatment of multidrug-resistant HIV-1 infection in adults and PrEP in both adults and adolescents.[18]

For the treatment of multidrug-resistant HIV-1 infection, it is recommended to be used in combination with other antiretroviral drugs such as emtricitabine and tenofovir. It is specifically indicated for patients with failing ART regimens because of resistance, intolerance or other safety concerns.[19]

The significance of lenacapavir registration in South Africa is for PrEP; and approved for reducing the risk of HIV-1 infection in adults and adolescents weighing at least 35 kg. High risk groups of clients who are encouraged to take up PrEP include female sex-workers, men having sex with men, pregnant and breastfeeding women and adolescent girls. For these populations, lenacapavir could reduce the stigma of visible medication use, improve autonomy and unstable access to healthcare, and eliminate barriers related to daily pill burden.[9] The long-acting sub-cutaneous injection offers a convenient alternative to daily oral PrEP in both high and low-resource settings. Lenacapavir PrEP is highly effective at preventing HIV acquisition, and the long-acting option may increase the uptake of HIV prevention strategies.[11]

The efficacy of lenacapavir has been shown with the PURPOSE 1 and PURPOSE 2 trials, where lenacapavir was evaluated against daily oral PrEP and not a placebo. Lenacapavir showed a reduction of new infections in 99%, displaying one of the lowest incidence rates in any HIV trial.[9]

Clinical guidance for using lenacapavir as PrEP

Identifying eligible candidates for PrEP

Clinicians, pharmacists or registered nurses providing PrEP services should first assess the client's HIV acquisition risk and exclude those with acute HIV infection.[20]

Recommended laboratory testing

Laboratory blood-based HIV antigen/antibody testing is recommended on initial lenacapavir injection to rule out recent HIV infection but may be administered if testing occurred within the previous seven days. At initiation of lenacapavir PrEP, a confirmatory HIV RNA test should be obtained, although the RNA assay should not delay treatment initiation. A repeat antigen/antibody test should be obtained after four weeks to exclude undetected baseline infection. For patients with positive antigen/antibody tests, a full HIV test panel should be performed and first-line ART initiated.[20]

Hepatitis B viral (HBV) infection should be ruled out if patients are switched from tenofovir-based PrEP to lenacapavir, as tenofovir suppresses HBV. Alternative treatment for HBV should be provided.[20]

Initiation and dosing regimen

Once a client is deemed eligible for PrEP with lenacapavir, the client can be initiated immediately with a loading dose. Figure 2 provides a visual representation of the dosing regimen, which

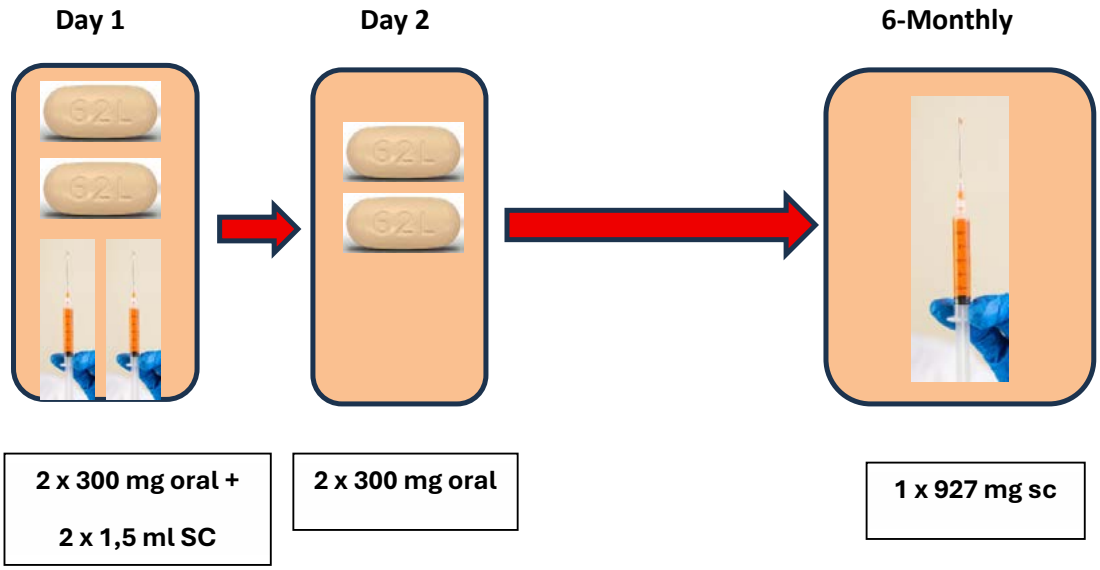

Figure 2: Dosing regimen for lenacapavir PrEP

includes two 300 mg oral tablets and two 1.5 ml subcutaneous injections (927 mg), administered at least 4 inches apart on day one. Injection sites include the abdomen or anterior thigh. Day 2 is followed by two 300 mg tablets, whereafter the subcutaneous injections can be administered 927 mg every six months.[11,20]

Side effects, adverse events and contraindications

Several studies have assessed the efficacy and safety aspects related to the use of lenacapavir.[8,17,21-23] In terms of efficacy, long-acting lenacapavir has overall been proven to be highly effective in preventing HIV acquisition and in achieving viral suppression in heavily previously treated people with multidrug-resistant HIV.[8,23] However, the use of lenacapavir is associated with injection site reactions such as pain, swelling, erythema, induration and nodules.[20-23] Nodules are the most reported injection site reaction and are formed because of the drug depot that results in a subcutaneous nodule. It can be several centimetres in size and may last from several months to more than a year.[20] Other injection site reactions usually resolve within a couple of days and are mild.[22] Other non-injection site side effects include nausea, diarrhoea, cough, headache, pyrexia, urinary tract infections, arthralgia, back pain, constipation, rash and oral candidiasis.[8,17,22]

Although lenacapavir has no safety concerns and has been shown to be safe to use in pregnancy, it may lead to an increased risk of resistance to capsid inhibitors among those who experience a breakthrough infection.[23] This resistance is due to seven mutations (L56I, M66I, Q67H, K70N, N74D, N74S, and T107N) that have been identified in the HIV-1 capsid protein.[24] However, lenacapavir resistance remains a rare occurrence, even in monotherapy, and has only been observed at subtherapeutic levels.[24]

Lenacapavir has significant interactions with inducers of CYP3A and UGT1A1 enzymes, such as rifampicin, anticonvulsants, carbamazepine, phenytoin, and St. John's wort. This is an aspect that should be considered in TB-co-infection. Some of these CYP3A4 inducers are antiretrovirals, for example, efavirenz, nevirapine, and etravirine, as well as tipranavir/ritonavir.[18] These drugs reduce the pharmacokinetic exposure of lenacapavir when used simultaneously; therefore, they are contraindicated. Additionally, caution should be practiced when starting lenacapavir after stopping these strong inducers, as their effects can last for weeks, and an interval of four weeks is recommended before initiating lenacapavir.[18]

Role of a pharmacist

Pharmacists can play an essential role in promoting the safe, effective, and rational use of lenacapavir in both HIV treatment and prevention settings. These include assessing patient eligibility by reviewing HIV status, patient resistance profiles, and concomitant use of other medications to minimise potential drug-drug interactions, particularly due to lenacapavir's involvement with CYP450 enzymes.[25,26] Pharmacists are also responsible for monitoring adverse drug reactions, with particular attention to injection site reactions, such as pain, swelling, and erythema associated with the long-acting formulation. In addition, pharmacists provide essential patient education on the importance of maintaining the six-month dosing schedule, as delayed or missed doses may compromise therapeutic effectiveness.

From a stewardship perspective, pharmacists promote the rational use of lenacapavir to minimise the risk of resistance development and ensure alignment with current HIV treatment and prevention guidelines.[10] Furthermore, pharmacists contribute to pharmacoeconomic decision-making by evaluating the cost-effectiveness of long-acting therapies compared with conventional daily regimens, which is especially relevant in settings with limited resources. Through these roles, pharmacists support improved clinical outcomes, enhance adherence, and strengthen public health efforts aimed at reducing HIV transmission.

Conclusion

Lenacapavir marks an important advancement in HIV care by addressing some of the key issues and difficulties associated with traditional antiretroviral therapy. Its unique capsid inhibitor mechanism and long-acting formulation offer a more convenient option for HIV prevention and treatment for patients, particularly those with multidrug-resistant HIV-1 or difficulty maintaining daily adherence. However, lenacapavir is not a cure for HIV, but it controls viral replication and reduces the risk of progression to AIDS. For PrEP, lenacapavir should be used in addition to comprehensive HIV prevention strategies, including regular testing and safe sex practices. While lenacapavir is generally well tolerated, with mostly mild injection site reactions, attention must still be paid to possible drug interactions and the risk of resistance if drug levels are not adequately maintained. Pharmacists play a vital role in supporting its safe and effective use through patient counselling, monitoring, and promoting adherence. Overall, lenacapavir provides a promising and practical alternative that could improve patient outcomes and strengthen ongoing efforts to control the HIV epidemic.

ORCID

KP Selomo https://orcid.org/0009-0008-7708-9644

NM Moloto https://orcid.org/0009-0003-3984-2387

MJ Luvhimbi https://orcid.org/0009-0009-1244-8068

E Bronkhorst https://orcid/org/0000-0002-6872-5417

References

1. Jacobson K, Ogbuagu O. Integrase inhibitor-based regimens result in more rapid virologic suppression rates among treatment-naïve human immunodeficiency virus-infected patients compared to non-nucleoside and protease inhibitor-based regimens in a real-world clinical setting: A retrospective cohort study. Medicine. 2018;97(43):e13016. https://doi.org/10.1097/MD.0000000000013016.
2. Swinkels HM, Nguyen AD, Samandari T, Gulick PG. HIV and AIDS. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026. Available from: https://www.ncbi.nlm.nih.gov/books/NBK534860/. Accessed 19 March 2026.
3. Scarsi KK, Swindells S. The promise of improved adherence with long-acting antiretroviral therapy: What are the data? J Int Assoc Provid AIDS Care. 2021;20:23259582211009011. https://doi.org/10.1177/23259582211009011.
4. Fanjul F, Gavalda M, Campins A, et al. HIV therapy: The latest developments in antiviral drugs - a scoping review. Biomedicines. 2025;13(11):2629. https://doi.org/10.3390/biomedicines13112629.
5. Goswami S, Veeramachaneni S, Masurkar PP. Lenacapavir for HIV PrEP: Narrative review of clinical trials and implications for patient access. Curr Treat Options Infect Dis. 2025;17:5. https://doi.org/10.1007/s40506-024-00281-2.
6. Link JO, Rhee MS, Tse WC, et al. Clinical targeting of HIV capsid protein with a long-acting small molecule. Nature. 2020;584(7822):614-8. https://doi.org/10.1038/s41586-020-2443-1.
7. Demirdjian S, Naik V, Margot N, Falkard B, Callebaut C. Phenotypic characterisation of replication-impaired lenacapavir-resistant HIV clinical isolates. J Med Virol. 2025;97(4):e70340. https://doi.org/10.1002/jmv.70340.
8. Ogbuagu O, Molina JM, Chetchotisakd P, et al. Efficacy and safety of long-acting subcutaneous lenacapavir in heavily treatment-experienced people with multidrug-resistant HIV-1: Week 104 results of a phase 2/3 trial. Clin Infect Dis. 2025;80(3):566-74. https://doi.org/10.1093/cid/ciae423.
9. Miteu GD. Lenacapavir and global HIV prevention: A breakthrough at risk of leaving millions behind. Ann Med Surg. 2026;88(3):2462-6. https://doi.org/10.1097/MS9.0000000000004783.
10. World Health Organization. Guidelines on lenacapavir for HIV prevention and testing strategies for long-acting injectable pre-exposure prophylaxis [Internet Who.int.]. World Health Organization; 2025. Available from: https://www.who.int/publications/i/item/9789240111608. Accessed 20 March 2026.
11. South African Health Products Regulatory Authority. SAHPRA Registers Lenacapavir. In News & Updates, Press Releases; 2025.
12. Ma C, Chang J, Yu B. Sunlenca® (lenacapavir): A first-in-class, long-acting HIV-1 capsid inhibitor. Acta Pharm Sin B. 2024;14(12):5512-4. https://doi.org/10.1016/j.apsb.2024.08.009.
13. Canales E, Tse W, Schroeder SD, et al. Discovery of lenacapavir: First-in-class twice-yearly capsid inhibitor for HIV-1 treatment and pre-exposure prophylaxis. J Med Chem. 2025;68(20):21072-94. https://doi.org/10.1021/acs.jmedchem.5c01625.
14. McKellar MS. Lenacapavir: A first-in-class capsid inhibitor for HIV treatment and prevention. Curr Opin Infect Dis. 2025;38(3):208-13. https://doi.org/10.1097/QCO.0000000000001113.
15. Huang S-W, Briganti L, Annamalai AS, et al. The primary mechanism for highly potent inhibition of HIV-1 maturation by lenacapavir. PLoS Pathogens. 2025;21(1):e1012862. https://doi.org/10.1371/journal.ppat.1012862.
16. Hitchcock AM, Kufel WD, Dwyer KAM, Sidman EF. Lenacapavir: A novel injectable HIV-1 capsid inhibitor. Int J Antimicrob Agents. 2024;639(1). https://doi.org/10.1016/j.ijantimicag.2023.107009.
17. De Clercq E, Zhang Y, Li G, et al. Lenacapavir: A capsid inhibitor for HIV-1 treatment and prevention. Biochem Pharmacol. 2025;240:117125. https://doi.org/10.1016/j.bcp.2025.117125.
18. Di Perri G. Pharmacological outlook of lenacapavir: A novel first-in-class long-acting HIV-1 capsid inhibitor. Infez Med. 2023;31(4):495. https://doi.org/10.53854/liim-3104-8.
19. Drugs.com. Lenacapavir: Uses, dosage, side effects, warnings - drugs.com; 2026. Available from: https://www.drugs.com/lenacapavir.html.
20. Patel RR, Hoover KW, Lale A, et al. Clinical recommendation for the use of injectable lenacapavir as HIV preexposure prophylaxis - United States. MMWR Morb Mortal Wkly Rep. 2025;74:541-9. https://doi.org/10.15585/mmwr.mm7435a1.
21. Segal-Maurer S, DeJesus E, Stellbrink HJ, et al. Capsid inhibition with lenacapavir in multidrug-resistant HIV-1 infection. N Engl J Med. 2022;386(19):1793-803. https://doi.org/10.1056/NEJMoa2115542.
22. Hadia R, Patidar S, Kardani S, et al. A comprehensive review of the safety and efficacy of lenacapavir in the treatment of human immunodeficiency virus. J Young Pharm. 2024;16(1). https://doi.org/10.5530/jyp.2024.16.1.
23. Fonner V, Louis Charles K, Lee MT, et al. Web Annex B: Safety and efficacy of long-acting injectable lenacapavir as pre-exposure prophylaxis to reduce the risk of HIV acquisition: A systematic review. In: Guidelines on lenacapavir for HIV prevention and testing strategies for long-acting injectable pre-exposure prophylaxis (PrEP). Geneva: World Health Organization; 2025. https://doi.org/10.2471/B09477.
24. Margot N, Vanderveen L, Naik V, et al. Phenotypic resistance to lenacapavir and monotherapy efficacy in a proof-of-concept clinical study. J Antimicrob Chem. 2022;77(4):989-95. https://doi.org/10.1093/jac/dkab503.
25. Koren DE, Chahine EB, Sherman EM. Lenacapavir: A twice-yearly injectable for HIV pre-exposure prophylaxis. Ann Pharmacother. 2026;60(3):276-86. https://doi.org/10.1177/10600280251379877.
26. Marzolini C, Gibbons S, Seddon D, Khoo S. Drug-drug interactions potential with the HIV-1 capsid inhibitor lenacapavir. Expert Opin Drug MetabToxicol. 2025;21(2):161-72. https://doi.org/10.1080/17425255.2024.2415295.

Dispersible tablets: a promising dosage form for the administration of medicines to paediatric patients

N Smit, J Steenekamp, M Brits

Faculty of Health Sciences, Centre of Excellence for Pharmaceutical Sciences (Pharmacen™), North-West University, Potchefstroom, South Africa
Corresponding author, email: marius.brits@nwu.ac.za

Abstract

The lack of age-appropriate paediatric formulations remains a significant challenge in children's healthcare, resulting in decreased treatment safety, efficacy, and adherence. Children require individualised medicines because their growth, body functions, and developmental stages differ from those of adults. This review article focuses on the importance and challenges associated with designing paediatric dosage forms, the dosage forms currently available for children, the ideal considerations for these forms, and how dispersible tablets (DTs) meet each consideration, making DTs a promising option for children. Furthermore, the advantages and limitations of DTs are outlined, and the availability of DTs for paediatrics on the South African market is being investigated. DTs have recently emerged as an up-and-coming option for children as they combine the advantages of both liquid and solid formulations, offering accurate dosing, ease of administration, improved stability, and greater patient acceptability. Their ability to disintegrate rapidly in a small volume of liquid makes them especially suitable for children who have difficulty swallowing conventional tablets. By expanding the availability of DTs, both through local pharmaceutical development and the importation of internationally approved formulations, therapeutic outcomes in paediatrics can be improved by promoting safer and more effective paediatric medication use.

Keywords: dispersible tablets, paediatrics, safety, dosage forms

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Introduction

The development of paediatric-specific dosage forms is essential to promote medication adherence and achieve predictable pharmacological responses in children. It is important to provide formulations that are easy to administer, palatable, and flexible in dosing to improve compliance and therapeutic outcomes.[1] In recent years, the focus has shifted toward innovative oral dosage forms that address the paediatric-specific dosage form requirements, with dispersible tablets (DTs) emerging as a particularly promising option.[2]

Concerns about the availability of age-appropriate paediatric dosage forms

The lack of age-appropriate paediatric formulations remains an international concern for the safe and effective administration of medicine to this vulnerable patient group.[3] The persistent gap in evidence to guide the design of age-appropriate dosage forms has significantly slowed progress in paediatric formulation development.[4] Limited data are available on the acceptability of various dosage forms for children, including administration volume, dosage form size, smell and taste, and the safety of excipients in relation to age and developmental status.[3] In the past, treatment for children often relied on the off-label use of adult medications, prepared through extemporaneous compounding by pharmacists and caregivers. However, numerous concerns have been raised about this practice, as it may pose risks to quality, safety, and efficacy for the vulnerable paediatric population.[3,5] Furthermore, individual compounding and manipulation of medicines may be costly and time-consuming,[5] and many errors have been reported in the preparation of such medicines.[6] Reliance on compounding practices has increased as literature highlights numerous shortages in access to registered formulations in appropriate sizes and strengths for paediatric patients.[7-12] Factors contributing to these shortages include supply chain disruptions and limited interest in the production of paediatric-specific dosage forms by pharmaceutical manufacturers.[13]

Between January and March 2023, the European Confederation of Primary Care Paediatricians (ECPCP) conducted a survey to evaluate the availability of essential paediatric medicines. The survey recorded the responses of 640 paediatricians from 18 European countries. The survey highlighted shortages in paediatric-friendly formulations of commonly prescribed medicines. Due to these shortages, paediatricians in the survey were forced to use less appropriate alternatives, such as tablets and capsules designed for adult use. The results of this survey highlighted the urgent need for coordinated actions at multiple levels to address the shortage of essential paediatric medications.[7] The development of age-appropriate formulations that promote safe and effective administration and ensure adequate adherence remains a critical objective for health authorities and paediatric researchers.[14-16]

The number of formulations currently available for paediatric patients represents only a small fraction of the diverse range of treatments needed to effectively meet children's healthcare needs. The World Health Organization (WHO) reported that approximately 10% of medicines prescribed and used for children are either off-label or unlicensed, indicating the need for paediatric-appropriate

medicines.[1] According to Kaushal et al.,[17] approximately 7.5 million preventable medication errors occur annually among paediatric patients in the United States, with an estimated 14–31% of these errors resulting in serious harm or death.[18]

From a formulation perspective, in order to promote medicine adherence and acceptability, it is crucial for paediatric patients to have access to authorised and age-appropriate dosage forms.[6] The WHO highlighted the fact that "children are not little adults".[19] In 2007, the WHO initiated the "Make Medicines Child Size" (MMCS) campaign, encouraging countries to prioritise the procurement of medicines formulated in strengths suitable for the specific age or weight of children.[20] Thirteen years later, the global ecosystem for paediatric medicines was still underdeveloped and contributing to sluggish development of paediatric medicines.

In 2020, the WHO and founding members established the Global Accelerator for Paediatric Formulations (GAP-f) hosted network, in response to the World Health Assembly mandate to promote access to safe, effective and affordable medicines for children.[21] Despite the rapid pace of scientific and medical advances, in 2025 the WHO continued to express concern that the development of paediatric medicines remains behind. In an attempt to address this, GAP-f decided to roll out the 2025–2030 strategic roadmap, "Transforming the paediatric medicines ecosystem," with the mission of fostering collaboration among stakeholders to accelerate the research and development of medicines for children.[22] Other examples of internationally launched initiatives and legislation to promote access to paediatric medicines include the Paediatric Investigational Plans (PIP) in Europe and the Best

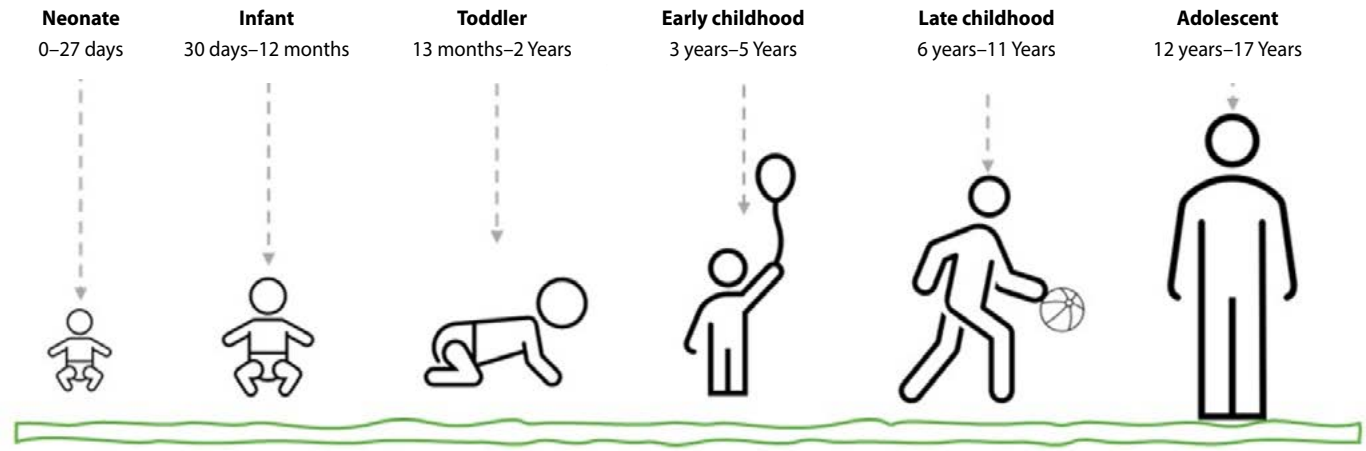

Figure 1: Different classes of the paediatric population. This figure is created based on the Munich Age Classification System (MACS)[25]

Table I: Challenges in developing paediatric-friendly formulations[20]

Factor	Challenges
Impact of growth and development on API ADME*	• Continuous physical and developmental changes during infancy and childhood • Progressive organ maturation occurring at various rates • Variations in body weight and surface area • Differences in pharmacokinetic and pharmacodynamic responses to substances • Adverse reactions varying with age • Disease may present differently in children when compared to adults
Registration of novel paediatric formulations	• Bioequivalence studies are usually performed in adult populations and extrapolated to paediatric populations • Regulatory and ethical challenges • Slow progress in the development of child-friendly dosage forms
Excipient safety and acceptability	• Increased toxicity and safety risks in preterm, term newborns, and infants younger than 6 months
Palatability and taste masking	• Unpleasant medicine taste is one of the main causes of treatment failure in children. Paediatrics often rejects bitter taste and prefers sweet taste • Inefficiency of sweeteners
Administration flexibility	• Lack of flexible solid oral dosage forms for the paediatric population
Tablet size	• Difficulties in swallowing large tablets or capsules • High dosage formulations limiting the ability to reduce tablet size • Individualised dosing
Onset of action and emergency situations	• Formulations having a long onset of action in emergency situations
Sustainability and economics	• Limited access to water, poor hygiene, heat, and high humidity in LMICs** • Potential risks during transportation • Improper use of medicines can contribute to drug resistance, extended hospital stays, and increased demand for healthcare resources.

* API ADME – Active pharmaceutical ingredient absorption, distribution, metabolism, and elimination
** Low- and middle-income countries

Pharmaceuticals for Children Act (BPCA) in the United States of America.[23,24]

In contrast to adults, where conventional dosage forms are generally highly accepted and tolerated, the acceptability of dosage forms in paediatric patients is more complex and depends on patient-specific characteristics such as age, competency, and developmental stage.[1] Thus, paediatric-specific formulations benefit children by providing safe and individualised medications.[3]

As illustrated in Figure 1, the paediatric population is a diverse group, ranging from neonates to adolescents.[25] These groups have significant physical and developmental differences in terms of pharmacokinetics and pharmacodynamics.[26] Developing a single formulation suitable for all paediatric age groups remains a significant challenge. As for adults, the guiding principle for selecting paediatric dosage forms should be the balance of risks and benefits, while taking into consideration the specific needs of this vulnerable population.[27]

Table I summarises the challenges that play a key role in the development of paediatric-friendly formulations. Addressing these challenges is essential to ensure the safety, efficacy, and acceptability of medicines intended for paediatric use.

Dosage forms currently available for paediatrics

Among all available administration routes, the oral route remains the most preferred as it allows painless administration and requires no specialised training.[3,26,28,29] In paediatric patients, the dosage forms commonly used for oral administration include solutions, syrups, suspensions, powders, granules, effervescent tablets, orodispersible tablets (ODTs), chewable tablets, mini-tablets, conventional immediate-release and modified-release tablets, and capsules.[15]

Although liquid dosage forms are commonly used in children, they have several disadvantages as they often contain excipients such as preservatives to ensure microbial stability or co-solvents to increase active pharmaceutical ingredient (API) solubility, which may be harmful in paediatrics. Additionally, when compared to solid dosage forms, liquid formulations tend to be more expensive.[30] In contrast, solid dosage forms offer long-term stability, accurate dosing, ease of transport and handling, and generally more cost-effective manufacturing, making them the formulation of choice within the pharmaceutical industry.[1,14,15] Unfortunately, despite their advantages, traditional solid oral dosage forms are typically not preferred in younger paediatric patients due to increased risk of choking and aspiration.[1,30,31] Additionally, unlike liquid dosage forms, traditional solid dosage forms lack dosing flexibility because they are available in fixed strengths and cannot be easily adjusted to provide a smaller, more precise dose.[32] Although splitting or breaking tablets is common, it does not always ensure accurate and consistent dosing.[33] This is a significant drawback, as paediatric patients require individualised dosing, often based on age and/or weight.[1]

The mentioned challenges can be addressed by tailoring dosage forms specifically for the paediatric population.[34] DTs and mini-tablets are currently emerging as promising alternatives to traditional solid oral dosage forms, offering easier administration and ingestion by younger paediatric patients.[2]

Paediatric-specific dosage form considerations

When designing an ideal dosage form, it is crucial to select the most suitable route of administration to ensure sufficient bioavailability and enable the API to achieve its intended therapeutic effect. Furthermore, the medicine should be designed to improve patient compliance by offering the least invasive route, minimising dosing frequency, and providing a simplified dosing regimen.[35] An ideal dosage form, whether for children or adults, would also be one that does not require special storage conditions, complies with regulatory quality standards, exhibits minimal side effects, is easy to administer, and can be manufactured cost-effectively. The oral route best meets the aforementioned criteria.[35]

Patient-related factors, including age-specific preferences (i.e., colour, appearance, smell, texture, taste, and swallowability of the medicine), as well as disease states and disabilities, should be considered when designing paediatric dosage forms. Furthermore, factors related to the children's guardians should also be considered, as the success of administering the medicine is as important as the medicine's quality and suitability. Guardian-related factors include ease and convenience of administration, dose flexibility, and the ability for the child to have the medicines administered at school if needed.[1,14]

Dispersible tablets as a promising dosage form for paediatric patients

Dispersible tablets - a flexible solid oral dosage form

Current research on paediatric formulation development mainly focuses on solid oral dosage forms that are easily swallowed by children.[14,15] The WHO recommends that flexible solid oral dosage forms should be developed and used in paediatric patients.[16,36] Flexible solid oral dosage forms are defined as a solid dosage form that can be administered to patients in more than one manner (i.e., may be dispersed or taken orally as a whole).[30,36] Flexible solid oral dosage forms include ODTs, chewable tablets, and soluble or DTs.[1,30] Flexible solid oral dosage forms help to overcome swallowing difficulties faced by paediatric patients, as they are formulated to disintegrate either in the mouth or in an external liquid (such as water or breast milk) prior to swallowing.[37] Additionally, these dosage forms offer the combined advantages of both conventional liquid and solid formulations.[38]

DTs are emerging as a suitable dosage form for administering medicine to paediatric patients. The British Pharmacopoeia (BP) defines DTs as "Uncoated or film-coated tablets intended to be dispersed in water before administration, giving a homogeneous dispersion."[39] A dispersible tablet is typically dispersed in about 5–15 mL of water before administration.[31] This low dispersion

volume makes it ideal for administration to younger paediatric patients.[1] DTs can thus be regarded as a model flexible dosage form, since they are produced and stored in the solid state, with only a single dose converted into a liquid at the time of administration. This improves chemical stability by keeping the remaining doses in solid form until required, offering the combined benefits of both solid and liquid formulations.

Dispersible tablets – ticking all the right boxes

Table II outlines the ideal considerations for paediatric dosage forms and demonstrates how DTs meet these requirements, making DTs one of the most suitable dosage forms for paediatric patients. Further details on specific considerations have been supplied to clarify or enhance the content of Table II.

The safety profile of the excipients used in the manufacturing of DTs differs from that of the excipients used in other paediatric dosage forms in terms of the type, number and functions of excipients required. Typical excipient classes included in DT formulations include diluents, disintegrants, binders, lubricants, and sweeteners/flavourants. These excipients are usually present in relatively low quantities when compared to those excipients used in liquid formulations (i.e., solvents, cosolvents, preservatives, sweeteners/flavourants, colouring agents, viscosity modifiers, buffers, surfactants and antioxidants). Concern has been raised with the use of common cosolvents (i.e., ethanol and propylene glycol), that resulted in acute life-threatening intoxication or cardiovascular, respiratory side effects, and hepatic toxicity in newborns and infants.[50] In formulating DTs, the potential exposure to these hazardous cosolvents is avoided, thus contributing to a safer dosage form for paediatric patients. The use of certain bactericidal preservatives in liquid oral formulations, such as benzalkonium chloride, has raised concern because they have been linked to paradoxical bronchospasm in asthmatic children.[51] During the manufacturing of DTs, the inclusion of preservatives is not necessary, thereby reducing children's risk of exposure.

The excipients used in effervescent tablets are generally acceptable in adult formulations; however, they may be unsuitable for use in young children.[52] The use of effervescent tablets in paediatric patients – especially premature babies or low-birth-weight infants – is not recommended, as they often contain high concentrations

Table II: Ideal considerations for paediatric dosage forms,[1,14,40] and how DTs comply with these considerations

Consideration	How DTs comply with each consideration
Accurate and convenient dose measurement	DTs offer advantages such as accurate dosing.[29] DTs need to comply with the pharmacopoeial requirements of uniformity of dosage units, which promotes dose accuracy and uniformity.[41] However, they are typically available in fixed-strength formulations, which limits dosage flexibility and poses challenges for individualised dosing.[32]
Convenient, easy, and reliable administration	DTs may be swallowed as whole units, which is commonly preferred by paediatric patients older than six years. Furthermore, it is suitable for patients who experience difficulty swallowing conventional tablets (patients younger than 3 years),[42] and it can be prepared by caregivers (disintegrating within 3 minutes) without the need for specialised equipment or training.[28]
Safe and well-tolerated excipients are included in the formulation	The safety profile of excipients used in DTs differs from that of other paediatric dosage forms due to differences in the types, quantities, and functions of the required excipients. DT excipients are generally used in smaller amounts compared to the wide range of excipients used in liquid oral formulations. Furthermore, the excipients used in the manufacturing of DTs are widely used in solid oral dosage forms, and extensive toxicological data supporting their safety are available. The manufacturing of DTs offers an ideal opportunity to exclude high-risk excipients, such as co-solvents, preservatives, surfactants, and other additives, which have been associated with serious toxicity and adverse side-effects in newborns and infants. Only excipients proven safe at the intended paediatric exposure are accepted by regulatory agencies for inclusion in DTs.[15]
Reduced number of excipients is included	Unlike liquid formulations, which may contain numerous excipients to enhance the API solubility or maintain microbial stability, solid dosage forms such as DTs do not require these additional excipients, making them a safer option for paediatric use.[30] Using multifunctional and co-processed excipients in the manufacturing of DTs may simplify formulation, improve manufacturability and enhance product performance and acceptability.
Organoleptic acceptability of the medicine to the paediatric patient	Small quantities of flavourings and sweeteners may be incorporated to improve the organoleptic acceptability of DTs by paediatric patients.[43] Other taste-masking technologies, such as ion-exchange resins[44] and coating of API particles[45] may also be utilised in dispersible tablet formulations to mask the taste of bitter-tasting APIs. Proper dispersion of DTs promotes the formation of a uniform suspension that has a smooth mouth feel without any gritty particles.[46]
DTs have the potential to be a 'One dosage form fit for all' dosage form	As mentioned, DTs are typically available in fixed-strength doses, which limit dosage flexibility and, in turn, individualised dosing adjustments.[32] Therefore, for individualised dosing, a DT (if suitably formulated) could potentially be dispersed in a known volume of liquid, and the required dose is administered by only administering a proportional volume of the dispersion to the patient.
The dosage form is manufactured using simplified manufacturing processes	Conventional manufacturing methods such as direct compression, dry granulation, and wet granulation have all been used to manufacture DTs, supporting scalability and cost reduction.[31] DTs may also be manufactured using more advanced manufacturing processes (i.e., lyophilisation, tablet moulding, spray drying, 3D-printing, etc.) to accommodate APIs with varying physicochemical properties (refer to versatility in the selection of manufacturing processes suitable for DTs).
The final product should exhibit suitable physical, chemical and microbiological stability	DTs are formulated in solid form and, therefore, present with greater physical, chemical and microbiological stability than liquid formulations,[47] thus presenting with longer shelf life[48] and reduced cold-chain dependence.[49]

of sodium, which cannot be effectively cleared from their bodies due to their immature hepatic and renal systems.[53]

In recent years, several databases and initiatives have been established to support the selection of suitable and safe excipients for use in the manufacture of paediatric dosage forms. Some of these databases and initiatives include ACToR (Aggregated Computational Toxicology Resource),[54] STEP (Safety and Toxicity of Excipients for Paediatrics), PERA tool (Paediatric Excipient Risk Assessment Tool)[55] and EuPFI (European Paediatric Formulation Initiative).[56] Excipient selection in paediatric formulations should be guided by safety considerations, regulatory requirements/recommendations, and the need to minimise exposure to excipients associated with potential side effects. These tools can support the selection of the most suitable excipients for a risk-based formulation of paediatric-friendly DTs.

A reduced excipient load can be achieved by employing multifunctional excipients that serve more than one function within the formulation. This reduced burden may not only decrease the number of excipients needed in the formulation but also simplify the manufacturing process. A classic example of a multifunctional excipient is mannitol, which is frequently used in DT formulation as a water-soluble diluent which also enhances patient acceptability due to its mild sweetness and cooling mouthfeel. Microcrystalline cellulose is another example used as a filler with binding, lubricating and disintegrating properties.[53] Using multifunctional excipients has the added benefit of reducing unnecessary excipient exposure in paediatric patients.

The application of co-processed excipients (i.e., a combination of two or more excipients prepared by spray-drying, co-crystallisation or wet granulation) for the manufacturing of directly compressible DTs benefits not only the patient (due to improved organoleptic qualities and enhanced palatability) but also presents with manufacturing benefits such as reduced manufacturing processes, reduction in processing and manufacturing time, improved batch-to-batch reproducibility, and reduced excipient variability.[57-59] The ability of various co-processed excipients to improve manufacturability and patient acceptability of DTs has been investigated and reported in the available literature.[58,59] Unlike liquid oral dosage forms, solid oral dosage forms are not susceptible to the physical instabilities associated with liquids, such as crystallisation or precipitation of the API, sedimentation, phase separation, and solvent-mediated polymorphic transformation.[60-62] As a solid dosage form, DTs may exhibit greater chemical stability than liquid dosage forms due to the absence of an aqueous medium, which can facilitate API hydrolysis.[63] Liquid oral dosage forms are also more prone to microbiological instability as aqueous vehicles provide an ideal environment for the growth of yeasts, moulds and microbes.[64]

Moreover, DTs offer an additional advantage in that they can be administered via the nose using a nasogastric tube. Nasogastric administration is especially useful for patients requiring assisted feeding, such as neonates and infants, as well as critically ill patients. Examples of commercially available DTs which can be administered through a nasogastric tube include Finlee 10 mg DT,[65] Brilique 90 mg ODT,[66] and Spritam®.[67]

In the WHO guideline "Points to consider in the formulation of paediatric medicines," the WHO urges the development of flexible dosage forms for children, referring to DTs as a suitable example.[68]

Advantages and limitations of dispersible tablets

The use of DTs in paediatric patients offers promising and unique benefits:

- They are particularly appropriate for patients with swallowing difficulties, like neonates and infants.
- The rapid disintegration facilitates the dissolution and absorption of the API, leading to a quick onset of therapeutic effect.
- DTs offer advantages over chewable tablets since they can be useful for children who have lost their primary teeth but do not yet have all their permanent teeth.
- DTs reduce the risk of asphyxiation associated with oral administration of traditional formulations, offering greater safety, especially in paediatric patients.
- DTs offer greater convenience and transportability compared to liquid preparations because they do not require any refrigeration, unlike some liquid formulations.
- As a solid dosage form, it exhibits enhanced chemical stability compared to liquid preparations.
- Traditional solid oral dosage form manufacturing processes can be employed, thereby lowering the associated production costs.

However, DTs may also have some limitations:

- DTs for suspension/solutions tend to have hygroscopic qualities and may therefore require specialised packaging to provide additional moisture protection, ensuring product integrity.
- DTs may have a higher friability and lower hardness than traditional tablets, making them fragile and difficult to handle, often requiring special packaging in peel-back blisters. However, increased mechanical strength usually prolongs disintegration time, so it is important to find a suitable balance between these factors.
- APIs with an unpleasant taste should undergo effective taste masking to prevent the API's taste from remaining in the oral cavity.
- DTs require water for administration.
- DTs are formulated as a fixed-dose dosage form, presenting with limited dosing flexibility.[31,69,70]

Versatility in the selection of manufacturing processes suitable for dispersible tablets

Conventional (and cost-effective) manufacturing methods such as direct compression, dry granulation, and wet granulation have all been employed in the past in the production of DTs.[31] These techniques are widely used due to their scalability, regulatory

Table III: Example of manufacturing processes that may be employed to produce DTs and the scenarios in which they are most suitable

Manufacturing process	Scenarios when the manufacturing process is most suitable
Direct compression	• API is sensitive to heat and moisture[73] • API-excipient blend exhibits good flow and compressibility properties[74] • API does not exhibit pressure-sensitive polymorphic transitions[75] • Formulation requires a low dose loading per unit, as most APIs exhibit poor compressibility and flowability, necessitating the addition of excipients to address these issues[76]
Dry granulation	• API is sensitive to moisture (i.e., susceptible to hydrolysis) or heat[73] • Non-granulated API-excipient blend exhibits poor flow properties[77] • API does not exhibit pressure-sensitive polymorphic transitions[75]
Wet granulation	• API does not exhibit moisture or heat sensitivity[73] • Non-granulated API-excipient blend exhibits poor flow or compressibility properties[78] • When content uniformity is required for low-dose (i.e. potent) APIs[79] • API does not exhibit moisture, heat or pressure-sensitive polymorphic transitions[80] • Formulation requires a high dose loading per unit[81]
Lyophilisation (Freeze-drying)	• When the API is extremely sensitive to heat or moisture[82] and also when rapid disintegration of the DT is required[83] • Formulation requires a low dose loading per unit (< 60 mg)[31] • Lyophilisation allows for the inclusion of API presented as nanoparticles in tablets. This process keeps the nanoparticles intact, controlling API release, whereas compression results in breakage of the nanoparticles[84] • The freeze-drying process can convert crystals of poorly water-soluble API into an amorphous form with smaller particles, leading to enhanced solubility and dissolution performance[85]
Tablet moulding	• Formulations which require high porosity and quick dispersion[86] • API is water-soluble and not sensitive to heat[87]
Spray drying	• Formulations where the API has poor aqueous solubility[88] • Suitable where rapid tablet disintegration is required
Sublimation	• Removal of volatile substances to create a porous tablet structure[89] • API is compatible with volatile subliming agents such as camphor and menthol[90] • Suitable when rapid disintegration is required[89]
3D-printing	• Personalised medicine or customised doses are required[91] • When the API does not exhibit heat sensitivity, methods such as fused deposition modelling can be used, whereas heat-sensitive APIs can be used in methods such as semi-solid extrusion[92]

familiarity, and suitability for industrial manufacturing. More advanced manufacturing techniques, such as lyophilisation or freeze-drying, tablet moulding, spray drying, and sublimation, have also been utilised, enhancing the versatility of manufacturing processes.[31] These innovative methods enable the production of highly porous structures and result in rapid disintegration.[71]

DTs can furthermore be manufactured using emerging technologies such as 3D-printing. This approach allows precise control over tablet design and flexible dose adjustments. As a result, this method enables the manufacture of personalised or customised dosage forms tailored to the needs of individual paediatric patients.[72] Table III summarises examples of manufacturing processes that may be used in the production of DTs and the scenarios in which each process is most suitable.

Availability of dispersible tablets for paediatric use

The table below offers an overview of various DT formulations currently available in South Africa for paediatric use. This underscores the increasing availability of DT formulations for commonly used APIs in paediatric patients. By displaying the range of APIs formulated as DTs, the table also highlights the growing recognition by manufacturers and regulatory authorities of the importance of developing age-appropriate medicines for the paediatric population.

As shown in Table IV, commercially available paediatric DTs in South Africa include APIs from the following therapeutic classes: antiretroviral (ARV) agents, antivirals, antihistamines, ammonia-detoxicants, iron chelators, non-steroidal anti-inflammatory drugs (NSAIDs), antiemetics, antidiarrheal agents, antitubercular agents, and antipsychotics. However, globally, paediatric DTs are available for APIs in the following therapeutic classes: antibiotics,[93,94] analgesics,[95,96] leukotriene receptor antagonist (LTRA),[97] proton pump inhibitor (PPI),[98] mineral supplement,[99,100] antimalarial,[101,102] NSAID,[103-105] antiemetic,[106] anti-histamines.[107] To address the current therapeutic gaps in paediatric DT availability in South Africa, importing suitable and approved DTs from international markets could be a practical short-term solution. In the longer term, these gaps should encourage the local pharmaceutical industry to invest in developing and registering new paediatric DT formulations, ensuring a wider range of safe and accessible treatment options for children.

Conclusion

DTs are an innovative advancement in the use of solid oral dosage forms. The greater patient compliance that DTs offer over conventional dosage forms, together with their convenience, effectiveness, and rapid onset of action, has drawn the interest of numerous manufacturers over the past decade. DTs are considered a superior dosage form, and ongoing research and

Table IV: DT formulations currently available on the South African market for paediatric use

API(s)	Examples of registered products in SA	Age of the intended patient	Reference
Abacavir/Lamivudine	Dumiva dispersible, Divudine 60/30 dispersible tablet and Divudine 120/60 dispersible tablet	≥ 3 months	108, 109
Acyclovir	Acitab DT 200 / 400 / 800 DT	2 years and younger	110
Bilastine	Ilaxten ODT	≥ 6 years	111
Carglumic acid	Carbaglu	From birth	112
Deferasirox	Siroxtrin 125, 250 & 500, Exjade	≥ 2 years	113, 114
Diclofenac sodium	Cataflam-D, Diclo-flam Blackcurrent	≥ 14 years	115, 116
Dolutegravir	Ristegra dispersible tablets	≥ 4 weeks	117
Dolutegravir as Dolutegravir Sodium	Tivicay 5 mg	≥ 4 weeks	118
Domperidone	Motivom 10 ODT	≥ 12 years	119
Loperamide Hydrochloride	Imodium® Melt	≥ 6 years	120
Piroxicam	Rheugesic	≥ 12 years	121
Rifampicin and isoniazid	Ripyso Paed, Afaris Paed	≥ 28 days	122, 123
Rifampicin, isoniazid, and pyrazinamide	Co-Ripyso Paed 75/50/150	≥ 28 days	124
Risperidone	Ristabbs 0.5, 1 & 2, Zoxadon ODT	≥ 15 years	125, 126

local production efforts are essential to ensure broader access and affordability of these formulations to the paediatric population.

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ORCID

N Smit https://orcid.org/0009-0005-5153-7363

J Steenekamp https://orcid.org/0000-0002-4924-4423

M Brits https://orcid.org/0000-0003-0197-300X

References

1. Khan D, Kirby D, Bryson S, et al. Paediatric specific dosage forms: Patient and formulation considerations. Int J Pharm. 2022;616:121501. https://doi.org/10.1016/j.ijpharm.2022.121501.
2. Thomson SA, Tuleu C, Wong IC, et al. Minitablets: New modality to deliver medicines to preschool-aged children. Paediatrics. 2009;123(2):e235-8. https://doi.org/10.1542/peds.2008-2059.
3. Malkawi WA, AlRafayah E, AlHazabreh M, AbuLaila S, Al-Ghananeem AM. Formulation challenges and strategies to develop paediatric dosage forms. Children (Basel). 2022;9(4):488. https://doi.org/10.3390/children9040488.
4. Ranmal SR, Cram A, Tuleu C. Age-appropriate and acceptable paediatric dosage forms: Insights into end-user perceptions, preferences and practices from the Children's Acceptability of Oral Formulations (CALF) Study. Int J Pharm. 2016;514(1):296-307. https://doi.org/10.1016/j.ijpharm.2016.07.054.
5. van der Vossen A, Buljaç S, Akçay K, et al. Availability of age-appropriate paediatric formulations in the Netherlands: The need in daily clinical practice remains. Eur J Hosp Pharm. 2021;28(6):306-12. https://doi.org/10.1136/ejhpharm-2019-001977.
6. World Health Organization. FIP-WHO technical guidelines: Points to consider in the provision by health-care professionals of children specific preparations that are not available as authorised products. In WHO Technical Report Series, WHO, ed. 2016;996. Available from: https://www.who.int/publications/m/item/annex-2-trs-966. Accessed 16 March 2026.
7. Ejeta F, Feyisa D, Aferu T, et al. Rational dispensing of oral dosage forms of medicines to children and its associated factors in south west Ethiopia. Paediatric Health Med Ther. 2022;13:103-13. https://doi.org/10.2147/PHMT.S360383.
8. Cherchi A, Vaz A, Coelho A, Fregonese L, Thirstrup S. Tuberculosis medicines for children in Europe: An unmet medical need. ERJ Open Res. 2023;9(4):00730-2022. https://doi.org/10.1183/23120541.00730-2022.
9. Noguera-Julian A, Buonsenso D, McKenna L, Seddon JA, Ritz N. Availability of fixed-dose, child-friendly formulations of first-line tuberculosis drugs in Europe. Eur Respir J. 2021;58(3):2101196. https://doi.org/10.1183/13993003.01196-2021.
10. Chiumia FK, Chithope-Mwale C, Abikoloni F, et al. Availability, pricing, and affordability of essential medicines for paediatric population in Malawi. Front Pharmacol. 2024;15:1379250. https://doi.org/10.3389/fphar.2024.1379250.
11. Rautamo M, Kvarnström K, Sivén M, et al. A Focus group study about oral drug administration practices at hospital wards-aspects to consider in drug development of age-appropriate formulations for children. Pharmaceutics. 2020;12(2):109. https://doi.org/10.3390/pharmaceutics12020109.
12. Committee on Pediatric Studies Conducted Under the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA); Board on Health Sciences Policy; Institute of Medicine. Safe and Effective Medicines for Children: Pediatric Studies Conducted Under the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act. Field MJ, Boat TF, editors. Washington (DC): National Academies Press (US); 2012 Feb 29. PMID: 24872968. Accessed 16 March 2026.
13. Rosário A, Hankó B, Zelkó R. Managing drug shortages in paediatric care. Front Pharmacol. 2024;15:1416029. https://doi.org/10.3389/fphar.2024.1416029.
14. Nunn T, Williams J. Formulation of medicines for children. Br J Clin Pharmacol. 2005;59(6):674-6. https://doi.org/10.1111/j.1365-2125.2005.02410.x.
15. European Medicines Agency. Reflection paper: Formulation of choice for the paediatric population. 2006. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-formulations-choice-paediatric-population_en.pdf. Accessed 4 March 2026.
16. Kristensen HG. WHO guideline development of paediatric medicines: Points to consider in pharmaceutical development. Int J Pharm. 2012;2(435):134-15. https://doi.org/10.1016/j.ijpharm.2012.05.054.
17. Kaushal R, Goldmann DA, Keohane CA, et al. Adverse drug events in paediatric outpatients. Ambul Paediatr. 2007;7(5):383-9. https://doi.org/10.1016/j.ambp.2007.05.005.
18. Cowley E, Williams R, Cousins D. Medication errors in children: A descriptive summary of medication error reports submitted to the United States pharmacopeia. Curr Ther Res. 2001;62(9):627-40. https://doi.org/10.1016/S0011-393X(01)80069-2.
19. World Health Organization. Children are not little adults. In: WHO training package for the health sector: Children's health and the environment; 2019. Available from: https://iris.who.int/bitstream/handle/10665/331237/WHO-CED-PHE-EPE-19.12.07. Accessed 5 February 2025.
20. Golhen K, Buettcher M, Kost J, Huwyler J, Pfister M. Meeting challenges of pediatric drug delivery: The potential of orally fast disintegrating tablets for infants and children. Pharmaceutics. 2023;15(4):1033. https://doi.org/10.3390/pharmaceutics15041033.
21. World Health Assembly. Promoting innovation and access to quality, safe, efficacious and affordable medicines for children. World Health Organization. 2016;69:1-4. Available from: https://iris.who.int/handle/10665/252800. Accessed 16 March 2026.
22. World Health Organization. Transforming the paediatric medicines ecosystem. GAP-f Strategic road map 2025-2030. World Health Organization; 2025. Available from: https://iris.who.int/server/api/core/bitstreams/92efbc50-ce4a-4533-a065-66fa728bc278/content. Accessed 16 March 2026.
23. European Medicines Agency. Paediatric Investigations Plan (PIP); 2025. Available from: https://www.ema.europa.eu/en/human-regulatory-overview/research-development/

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Pharmaceutical application of selected polymers

J Wargula

Poznań University of Medical Sciences, Faculty of Pharmacy, Department of Organic Chemistry. ROR: https://ror.org/02zbb2597

Corresponding author, email: jkruk@ump.edu.pl

Abstract

The ubiquity of polymers in everyday applications also translates into their applicability in the broadly defined fields of medical and pharmaceutical sciences. Polymeric compounds find applications in ophthalmology, dentistry, orthopaedics, dermatology and plastic surgery. It is important to emphasise that they are used internally (e.g., endoprostheses, biodegradable scaffolds) and externally (e.g., so-called intelligent dressings, ointments, and creams). This publication presents basic polymers and their applications in pharmaceutical sciences. Their applications are outlined, among others, in chemical laboratories involved in drug synthesis, as drug carriers, and packaging production. Special attention is paid to the physico-chemical properties of polymers.

Keywords: polymer, application, pharmacy

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Introduction

Polymers are compounds of natural or synthetic origin that contain repeating elements called monomers in their structure.[1] We encounter them daily, for example, when using electronics, travelling, or shopping.[2-4] Polymers benefit from many medical specialities (including ophthalmology, dentistry, orthopaedics, surgery, and aesthetic medicine).[5-6] However, it is essential to emphasise the numerous applications of polymers in the pharmaceutical sciences. Polymers are used in the production of drug packaging and blisters, drug delivery systems, and as components of equipment used to produce medications.[7-9] Polymers can be found in research laboratories, where they are used in the form of personal protective equipment or plastic equipment components, but also where their dielectric and insulating properties, gas absorption, and pollutant adsorption properties are utilised.[10-13] This paper presents the usefulness of specific polymers in the pharmaceutical sciences. Particular emphasis was placed on the physicochemical properties that determine specific polymer applications, such as chemical resistance and surface properties. The article focuses primarily on publications from 2015–2025.

Application of selected polymers

Polyvinyl chloride

Polyvinyl chloride (PVC) is obtained industrially from ethene chloride (vinyl chloride). However, it should be emphasised that in the case of this polymer, great emphasis is placed on the ecological aspects of synthesis and biodegradation.[14] Plasticisers can modify physicochemical properties, which are currently divided into three groups depending on the degree of substitution of the original one used in the formulation process.[15] Such modifiable properties include, for example, mechanical strength, tensile strength, optical properties (e.g., in the case of ricinoleic acid derivatives), and antibacterial properties (e.g., in the case of imidazole-based ionic liquids).[15-17]

Due to its relatively inexpensive production process, this polymer is used to manufacture components that do not require sterilisation after use, such as syringes and probe components.[18] Additionally, PVC is transparent, biocompatible, and chemically resistant. PVC is also characterised by temperature stability up to approximately 60 °C. Pharmaceutical companies use PVC as mats, which are easy to keep clean, making them suitable for cleanrooms.[19] Furthermore, it is used to make cable channels or ion-selective half-cells used in divergent machines, e.g., refractometers, pH meters, and process-scale tangential flow filtration (TFF) systems.[20-21] Several different PVC products that contain di-2-ethylhexyl phthalate (DEHP) plasticiser are used in healthcare. Common products include feeding tubes, tubes and catheters, as well as infusion bags for nutrients or dialysis fluids.[22-23] This polymer is also ideal for producing disposable gloves and is an excellent alternative for people with latex allergies. It is also worth noting that various studies have been conducted on the safety of such gloves (e.g., drug permeation).[24-25] PVC can be found on pharmacy shelves in blister packs (especially for antibiotics, as the grey blister pack protects against light).[26-27]

Polyacrylates and polyacrylamides

These compounds are typically obtained through the free-radical polymerisation of acrylic acid derivatives. The polyacrylates are characterised by high transparency and chemical resistance; their flexibility depends on the monomer used. Polyacrylates are resistant to atmospheric aging, and their good optical properties are utilised in ophthalmology.[5] One representative of this group of compounds is sodium polyacrylate, which, thanks to its ability to absorb large amounts of water, is used in diaper absorbent pads. The carboxyl groups on this polymer face outward, allowing sodium ions to attract water and body fluids. This polymer also protects electrical cables and optical fibres.[28-29]

In the field of pharmaceutical sciences, the role of polyacrylamides is noteworthy. These compounds are produced through free-

radical polymerisation with appropriate amines and are used, among others, as electrophoresis gels, as thickeners in cosmetics, and in burn compresses.[30-32]

Above all, however, polyacrylamides are used in the production of therapeutic systems where drug release occurs at a programmed rate. Such systems ensure a constant drug concentration in the body, translating into greater treatment efficacy than traditional and long-acting forms. Transdermal polyacrylamides are used to treat conditions such as angina pectoris, motion sickness, pain, inflammation, hypertension, and nicotine addiction.[33-35] This polymer, in the form of hydrogels, is also used in oral therapeutic systems.[36-37]

Polyvinyl alcohol

A property of polyvinyl alcohol (PVA) used in pharmaceuticals is its ability to form hydrogels.[38] Many gelling agents exist, but boron compounds are among the most popular.[39] In addition to the applications in ophthalmic drops and therapeutic dressings discussed in previous publications, such hydrogels are also used in therapeutic systems.[40-42] Drug release from a hydrogel can occur in three possible ways:

a. diffusion (swelling leads to an increase in the spatial structure and the drug diffuses; the swelling rate can be regulated by changing pH or adding enzymes);
b. erosion (the polymer coating is destroyed, and the drug is gradually released);
c. leaching (the drug escapes the system through micropores; the coating is not destroyed).[40-42]

In the case of therapeutic systems, it is possible to manipulate their properties: the drug can be released under various circumstances, at a specific site, under the influence of temperature, radiation, or chemical factors.[43-44] The strictly therapeutic consequences include drug release at a particular site, prolonged action, and elimination of toxic concentrations (which is of great importance, for example, in cancer pharmacotherapy).[45-47]

Polytetrafluoroethylene

Polytetrafluoroethylene (PTFE) is typically produced by the free-radical polymerisation of tetrafluoroethylene. It is characterised by high chemical resistance and a high melting point.[48-49] These properties determine not only its most common use in the production of kitchenware (as a Teflon coating) but also its use as an insulator in drug packaging, which can be highly sensitive to atmospheric factors.[48-49]

PTFE has been used in the production of medical dressings. Its water resistance and air permeability provide a suitable environment for wound healing. These dressings are used in the treatment of, among other things, diabetic foot.[50-51]

Furthermore, PTFE has been used in the production of cosmetics as a bulking agent and lubricant.[52-54] It should also be emphasised that the safety of this polymer is widely discussed in the literature.[55-57]

Polylactide

This polymer is produced by single-step synthesis from lactic acid (generally resulting in a product with inferior properties and high mass) or by two-step synthesis: first, lactic acid is converted to lactide, and then polycondensation is formed.[58] Polylactide is characterised by low elasticity, stiffness, and brittleness.[59-60] Furthermore, this polymer shrinks under the influence of heat and is thermoplastic.[61]

In the pharmaceutical industry, polylactide is primarily used in drug delivery systems. Numerous modifications, such as pegylation, esterification (e.g., a cinnamic acid derivative), and combination with other substances (e.g., hydroxyapatite) or other polymers (e.g., glycolic acid), allow for the improvement of the properties of such systems.[62-64]

Polylactide formulations include hydrogels (e.g., curcumin), micelles (e.g., anticancer drugs), and nanoparticles (e.g., antibiotics).[65-67]

Alginates

Alginates are natural polymers containing a β-1,4-glycosidic bond obtained from algae.[68]

They have gained considerable popularity in the pharmacy market as specialised dressings. Alginates can form gels and absorb exudates. They are used as dressings to treat pressure ulcers and infected wounds due to their ability to remove dead tissue.[69-70]

Furthermore, heartburn medications containing alginates can be found on pharmacy shelves. The gel protects the stomach walls from gastric acid, while the other ingredients neutralise gastric contents. Their safety is confirmed because they are also administered to newborns.[71-73] Furthermore, alginates are used as iron chelators due to their ability to form coordinate bonds. Their chelating properties against heavy metals have also found several other applications, such as wastewater treatment.[74-75]

Another application of alginates in pharmaceutical sciences is as a material for microencapsulation, or the creation of drug forms enclosed in a special coating via *in situ* polymerisation. This form of drug administration allows for increased stability of the drug substance and its controlled release.[76-77]

Polysiloxanes

Polysiloxanes, compounds characterised by the presence of silicon in their structure, exhibit low surface tension and non-flammability.[78-79]

The first of these characteristics, low surface tension, has led to this polymer being used in shampoos, creams, and conditioners, including those recommended by dermatologists.[80-82]

In the form of the active ingredient (simeticone), this polymer can be found in flatulence medications. It does not affect gastric pH and has a protective effect.[83-84]

Polysiloxanes exhibit regenerative properties in the form of skin lotions.[85-86]

Another application of polysiloxanes is coating various items, such as tubes, where their anti-foaming properties are demonstrated. They are used to create feeding tubes, catheters, and heart-lung medical equipment for blood circulation.[87-88] They are also used as implant coatings, nanoparticles (np.) among others, in the production of bone implants or cochlear implants.[89-91]

Polyurethanes

Polyurethanes as polymers have many applications, including polyurethane adhesives and sponges.[92]

However, focusing on the medical and pharmaceutical potential, it is important to emphasise:

a. the potential use of polyurethane resin in bleeding control[93]

b. the creation of medical equipment94

c. its use in the production of dressings, where its biodegradability and unidirectional gas flow are exploited, accelerating the healing process.[95-96]

Polyurethanes are used as conjugates (e.g., with anticancer drugs) to produce drug delivery systems.[97-98] These polymers are used as nano- and microsystems, as well as membrane systems.[99-100] Using such systems, anticancer therapies and the treatment of bacterial infection become safer.[101]

Rubber

Natural rubber is obtained from the damaged tissues of rubber-bearing plants. It belongs to the group of polyterpenoids, and such a material can contain 35 000–320 000 isoprene units.[102]

Synthetic rubber, on the other hand, has been produced since the beginning of the 20th century and is characterised by:

a. solubility in hydrocarbons (including chlorinated hydrocarbons)

b. divergent chemical modification potential due to the presence of the C=C double bond, for example, hydrogenation, halogenation (mainly chlorination), epoxidation, and vulcanisation are possible

c. resistance to water, acids, and bases

d. elasticity and extensibility

e. flammability

f. lack of resistance to abrasion, ozone, and atmospheric factors.[103]

Therefore, rubber has found wide application, ranging from the rubber and clothing industries to the toy and sports industries. From a broad pharmaceutical perspective, agglutination tests are an interesting application besides their use in clothing and footwear production. Latex microspheres targeted to a specific substance or antigen are used in the detection of:

a. viruses (e.g., mumps)[104]

b. bacteria (e.g., tuberculosis, syphilis, cholera, plague)[105]

c. hormones (e.g., oestrogens)[106]

d. narcotics (e.g., cocaine, morphine)[107]

e. medications (e.g., barbiturates).[108]

Furthermore, latex is used as a carrier for substances with limited water solubility (e.g., anabolic steroids, hormonal compounds in contraception),[109] high toxicity (e.g., cyclophosphamide),[110] or in the production of vaccines (for malaria, tetanus).[111-113]

Polyglycolides

Polyglycolides are polymers of glycolic acid. Natural glycolic acid is found in sugarcane, beetroot, and pineapple. Potential medical applications include the production of resorbable surgical threads and sutures, which utilise polyglycolides' high extensibility and easy passage through tissues (so-called passage). These properties allow polyglycolides to produce dental floss for everyday use.[114-115]

Among the pharmaceutical applications of polyglycolides, drug delivery systems are worth mentioning. High hydrolytic stability, non-toxicity, and metabolism to neutral components (water, carbon dioxide; urinary excretion) ensure the safety of such therapeutic systems.[116-118]

Very often, in the form of a copolymer with polylactide, such systems produce vaccines.[119-120] Polyglycolide itself can be used in the form of blends or microspheres.[121-122]

Conclusions

The applications of polymers in the broadly defined pharmaceutical sciences can be divided into two basic groups: strictly laboratory applications and the broadly defined production of drugs, vaccines, tests, and materials for pharmaceutical applications.

Polymers are used as components of medical devices, laboratory equipment, and personal protective equipment for workers.

The second group of applications includes the production of drug packaging, the use of polymers as carriers for active substances and antigens, and their use as active substances (e.g., alginates). The properties of polymers that translate into specific preparations available on the pharmaceutical market include absorption (e.g., innovative dressings) and hydrophilic properties (e.g., eye drops, gels).

When it comes to the synthesis of new polymers and their exploration in pharmaceutical sciences, attention should be paid to protecting the natural environment and minimising the amount of waste generated (including PVC). In the field of pharmaceutical sciences, polymers can be explored for:

a. their use in drug delivery systems, especially antibiotics and anticancer drugs (e.g., polyacrylamides, polysiloxanes, polyglycolides, polyurethanes)

b. their use as carriers in vaccines (e.g., polyglycolides)

c. expanding the arsenal of available cross-linking agents (e.g., PVA)

d. their safety and thermoplasticity (e.g., PTFE, polylactide).

However, their biocompatibility and biodegradability should always be considered when synthesising new polymers with potential applications in the pharmaceutical sciences.

Conflict of interest

The author declares no conflict of interest.

ORCID

J Warguła https://orcid.org/0000-0002-7517-5345

References

1. Polymer. [Internet] [cited 2025 Dec 30]. Available from: https://www.britannica.com/science/polymer.
2. Ouyang J. Application of intrinsically conducting polymers in flexible electronics. SmartMat. 2021;2(3):263-85. https://doi.org/10.1002/smm2.1059.
3. Gupta P, Toksha B, Patel B, et al. Recent developments and research avenues for polymers in electric vehicles. Chem Rec. 2022;22(11):e202200186. https://doi.org/10.1002/tcr.202200186.
4. Verma SK, Prasad A, Sonika, Katiyar V. State of art review on sustainable biodegradable polymers with a market overview for sustainability packaging. Mater Today Sustain. 2024;100776. https://doi.org/10.1016/j.mtsust.2024.100776.
5. Warguła J. Nie tylko folie i opakowania. Część 1: O zastosowaniach polimerów w okulistyce, stomatologii i sprzęcie medycznym. Prospect Pharm Sci. 2024;22(4):135-45. https://doi.org/10.56782/pps.268.
6. Buchholz T, Siverino C, Moriarty TF, et al. Antibiotic-loaded polymer-calcium phosphate scaffold for treating orthopaedic device-related infection in a rabbit segmental bone defect model. J Biomed Mater Res - A. 2025;113(5):e37917. https://doi.org/10.1002/jbm.a.37917.
7. Çapkın İY, Gökelma M. A review on characterisation and recyclability of pharmaceutical blisters. Clean Waste Syst. 2023;4:100082. https://doi.org/10.1016/j.clwas.2023.100082.
8. Sung YK, Kim SW. Recent advances in polymeric drug delivery systems. Biomater Res. 2020;24(1):12. https://doi.org/10.1186/s40824-020-00190-7.
9. Ley SV, Fitzpatrick DE, Ingham RJ, Myers RM. Organic synthesis: March of the machines. Angew Chem Int Ed. 2015;54(11):3449-64. https://doi.org/10.1002/anie.201410744.
10. Kirschning A, Monenschein H, Wittenberg R. Functionalised polymers-Emerging versatile tools for solution-phase chemistry and automated parallel synthesis. Angew Chem Int Ed. 2001;40(4):650-79. https://doi.org/10.1002/1521-3773(20010216)40:4<650::AID-ANIE6500>3.0.CO;2-C.
11. Arabi M, Ghaedi M, Ostovan A, Wang S. Synthesis of lab-in-a-pipette-tip extraction using hydrophilic nano-sized dummy molecularly imprinted polymer for purification and analysis of prednisolone. JCIS. 2016;480:232-9. https://doi.org/10.1016/j.jcis.2016.07.017.
12. Dai D, Yang J, Zou YC, et al. Macrocyclic arenes-based conjugated macrocycle polymers for highly selective CO2 capture and iodine adsorption. Angew Chem. 2021;133(16):9049-57. https://doi.org/10.1002/ange.202015162.
13. Tan DQ. The search for enhanced dielectric strength of polymer-based dielectrics: A focused review on polymer nanocomposites. J App Pol Sci. 2020;137(33):49379. https://doi.org/10.1002/app.49379.
14. Iles A, Martin A, Rosen CM. Undoing chemical industry lock-ins: Polyvinyl chloride and green chemistry. In: Schummer J, Børsen T, editors. Ethics of chemistry: From poison gas to climate engineering. World Scientific Publishing Co Pte Ltd; 2021. p. 279-316. https://doi.org/10.1142/9789811233548_0011.
15. Czogała J, Pankalla E, Turczyn R. Recent attempts in the design of efficient PVC plasticisers with reduced migration. Materials. 2021;14(4):844. https://doi.org/10.3390/ma14040844.
16. Feng S, Jiang P, Zhang P, et al. Ricinoleic acid-based plasticiser with excellent optical properties for PVC polymers. Ind Crop Prod. 2023;199:116699. https://doi.org/10.1016/j.indcrop.2023.116699.
17. Zampino D, Mancuso M, Zaccone R, et al. Thermo-mechanical, antimicrobial and biocompatible properties of PVC blends based on imidazolium ionic liquids. Mater Sci Eng C. 2021;122:111920. https://doi.org/10.1016/j.msec.2021.111920.
18. Haishima Y, Isama K, Hasegawa C, Yuba T, Matsuoka A. A development and biological safety evaluation of novel PVC medical devices with surface structures modified by UV irradiation to suppress plasticiser migration. J Biomed Mater Res A. 2013;101(9):2630-43. https://doi.org/10.1002/jbm.a.34558.
19. Pham Le Q, Uspenskaya MV, Olekhnovich RO, Baranov MA. The mechanical properties of PVC nanofiber mats obtained by electrospinning. Fibers. 2021;9(1):2. https://doi.org/10.3390/fib9010002.
20. PVC in medical devices. Available from: https://wilmarcmedical.com/wp-content/uploads/PVC_Med_Devices_Karolinska.pdf. Accessed 30 Dec 2025.
21. What is PVC in the pharmaceutical industry. Available from: https://www.hs-plasticgroup.com/new_detail/What-is-PVC-in-the-pharmaceutical-industry.html. Accessed 30 Dec 2025.
22. PCV. Available from: https://www.mt.com/pl/pl/home/search/Advanced_Search.html#stq=PCV&stp=1&cat=PRODUCTS. Accessed 30 Dec 2025.
23. Cogent Lab Systems. Available from: https://hpcimedia.com/images/PDF/Cogent%20Lab%20Systems%20-%20Data%20Sheet%20-%20MS_DS8631EN.pdf. Accessed 30 Dec 2025.
24. Connor TH. Permeability of nitrile rubber, latex, polyurethane, and neoprene gloves to 18 antineoplastic drugs. Am J Health Syst Pharm. 1999;56(23):2450-53. https://doi.org/10.1093/ajhp/56.23.2450.
25. Wallemacq PE, Capron A, Vanbinst R, et al. Permeability of 13 different gloves to 13 cytotoxic agents under controlled dynamic conditions. Am J Health Syst Pharm. 2006;63(6):547-56. https://doi.org/10.2146/ajhp050197.
26. Sabee MM, Uyen NTT, Ahmad N, Hamid ZAA. Plastics packaging for pharmaceutical products. In: Hashmi MSJ, editor. Reference module in materials science and materials engineering. Elsevier: Amsterdam, The Netherlands; 2021. https://doi.org/10.1016/B978-0-12-820352-1.00088-2.
27. Górka T, Meisner M, Sarecka-Hujar B. Analysis of total hemispherical reflectance of pharmaceutical packaging containing cefuroxime. Available from: chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://sciforum.net/manuscripts/15918/manuscript.pdf. Accessed 23 Sept 2025.
28. Abd Manan TSB, Beddu S, Mohamad D, et al. Physicochemical properties of absorbent hydrogel polymers in disposable baby diapers. Chem Phys Lett. 2021;774:138605. https://doi.org/10.1016/j.cplett.2021.138605.
29. Tuteja J, Vyas A. Progressive approach of SAPs in disposable hygiene industry. In: Tuteja J, Vyas A, editors. Properties and applications of superabsorbent polymers: Smart applications with smart polymers. Singapore: Springer Nature Singapore; 2023. p. 171-81. https://doi.org/10.1007/978-981-99-1102-8_8.
30. Birtwistle MR, Huggins JR, Zadeh CO, et al. A 96-Well Polyacrylamide Gel for Electrophoresis and Western Blotting. bioRxiv [Preprint]. 2024 Nov 19:2024.05.10.593650. https://doi.org/10.1101/2024.05.10.593650. Update in: ACS Omega. 2025;10(10):10558-10566. https://doi.org/10.1021/acsomega.4c11137.
31. Safety assessment of polyacrylamide as used in cosmetics 2022. Available from: https://www.cir-safety.org/sites/default/files/RR_Polyacrylamide.pdf. Accessed 23 Sept 2025.
32. Babaluei M, Mottaghitalab F, Seifalian A, Farokhi M. Injectable multifunctional hydrogel based on carboxymethylcellulose /polyacrylamide /polydopamine containing vitamin C and curcumin promoted full-thickness burn regeneration. Inter J Biol Macromol. 2023;236:124005. https://doi.org/10.1016/j.ijbiomac.2023.124005.
33. Qia Z, Tran L, Parks J, et al. Highly stretchable gelatin-polyacrylamide hydrogel for potential transdermal drug release. Nano Select. 2021;2(1):107-15. https://doi.org/10.1002/nano.202000087.
34. Alex M, Alsawaftah NM, Husseini GA. State-of-all-the-art and prospective hydrogel-based transdermal drug delivery systems. Appl Sci. 2024;14(7):2926. https://doi.org/10.3390/app14072926.
35. Yang Y, Zhou R, Wang Y, et al. Recent advances in oral and transdermal protein delivery systems. Angewan Chem. 2023;135(10):e202214795. https://doi.org/10.1002/ange.202214795.
36. Pandey M, Choudhury H, D/O Segar Singh SK, et al. Budesonide-loaded pectin/polyacrylamide hydrogel for sustained delivery: Fabrication, characterisation and in vitro release kinetics. Molecules. 2021;26(9):2704. https://doi.org/10.3390/molecules26092704.
37. Musa Y, Musa H, Suleiman M, Yahaya S, Yahuza ZA. Polyacrylamide hydrogels for application in oral drug delivery. Nigeri J Sci Res. 2021;20(4):390-6.
38. Muppalaneni S, Omidian H. Polyvinyl alcohol in medicine and pharmacy: A perspective. J Dev Drugs. 2013;2(3):1-5. https://doi.org/10.4172/2329-6631.1000112.
39. Wang C, Shen Z, Hu P, et al. Facile fabrication and characterisation of high-performance Borax-PVA hydrogel. J Solgel Sci Technol. 2022;101:1-11. https://doi.org/10.1007/s10971-021-05584-0.
40. Peppas NA, Wright SL. Drug diffusion and binding in ionisable interpenetrating networks from poly (vinyl alcohol) and poly (acrylic acid). Eur J Pharm Biopharm. 1998;46(1):15-29. https://doi.org/10.1016/S0939-6411(97)00113-6.
41. Jensen BE, Dávila I, Zelikin AN. Poly (vinyl alcohol) physical hydrogels: Matrix-mediated drug delivery using spontaneously eroding substrate. J Phys Chem B. 2016;120(26):5916-26. https://doi.org/10.1021/acs.jpcb.6b01381.
42. Yari K, Gharati G, Akbari I. Evaluating effect of salt leaching method on release and swelling rate of metformin nanoparticles loaded-chitosan/polyvinyl alcohol porous composite. Int J Biol Macromol. 2023;227:1282-92. https://doi.org/10.1016/j.ijbiomac.2022.11.323.
43. Kouser R, Vashist A, Zafaryab M, Rizvi MA, Ahmad S. pH-responsive biocompatible nanocomposite hydrogels for therapeutic drug delivery. ACS App Bio Mater. 2018;1(6):1810-22. https://doi.org/10.1021/acsabm.8b00260.
44. Shaheen SM, Ukai K, Dai L, Yamaura K. Properties of hydrogels of atactic poly (vinyl alcohol)/NaCl/H2O system and their application to drug release. Polymer Int. 2002;51(12):1390-97. https://doi.org/10.1002/pi.1061.
45. Hussein Y, Loutfy SA, Kamoun EA, et al. Enhanced anti-cancer activity by localised delivery of curcumin form PVA/CNCs hydrogel membranes: Preparation and in vitro bio-evaluation. Int J Biol Macromol. 2021;170:107-22. https://doi.org/10.1016/j.ijbiomac.2020.12.133.
46. Rivera-Hernández G, Antunes-Ricardo M, Martínez-Morales P, Sanchez ML. Polyvinyl alcohol based-drug delivery systems for cancer treatment. Int J Pharmaceutics. 2021;600:120478. https://doi.org/10.1016/j.ijpharm.2021.120478.
47. Akhlaq M, Azad AK, Ullah I, et al. Methotrexate-loaded gelatin and polyvinyl alcohol (Gel/PVA) hydrogel as a pH-sensitive matrix. Polymers. 2021;13(14):2300. https://doi.org/10.3390/polym13142300.
48. Moll F, Bechtold-Peters K, Friess W. Evaluation of a novel silicone oil free primary pack-

Full list of references available on request

A review of patient knowledge and awareness regarding the use and storage of ophthalmic drops

D van Staden, S Gopaul

Department of Optometry, School of Health Sciences, University of KwaZulu-Natal, South Africa
Corresponding author, email: wallaced@ukzn.ac.za

Abstract

Background: Ophthalmic drops are a widely used pharmaceutical form for the treatment of ocular conditions. However, patient knowledge regarding the appropriate use and storage remains inconsistent and is often suboptimal. The aim was to determine the level of patient knowledge and awareness related to the correct usage and storage of ophthalmic drops, through a literature review.

Methods: Relevant studies published after the year 2000 were selected for review based on the inclusion criteria, focusing on patient knowledge and storage practices related to ophthalmic drops.

Results: Twenty-eight studies met the inclusion criteria, with an average sample size of 315 participants. Of these, fourteen studies involved glaucoma patients, two studies included postoperative cataract patients, two studies comprised of patients with both glaucoma and ocular hypertension, and ten studies involved patients with various ocular conditions that warranted the use of ophthalmic drops. To assess instillation techniques, nine studies employed video recordings, ten used questionnaires, five incorporated both methods and four studies were observational.

The results demonstrated that eyedrop administration remains a challenge among patients, resulting in bottle contact, inaccuracy and poor hand hygiene. The provision of education significantly improved technique in short-term follow-ups with improvements noted in accuracy, reduced contamination, and increased patient adherence. Poor eyedrop technique was noted in elderly patients, patients with low health literacy and in patients undergoing long-term therapy. Forgetfulness, inattentiveness, limited prior instruction, as well as physical and visual impairment were identified as attributers to correct eyedrop administration.

Conclusion: Patients lack knowledge and awareness on the use and storage of ophthalmic drops. Enhancing patient education is essential to improve understanding and correct practices of ophthalmic drop administration.

Keywords: pharmaceutical, literature review, ophthalmic drops, usage, techniques, storage, therapeutic outcomes

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Introduction

Visual impairment remains a global health challenge, primarily caused by conditions such as uncorrected refractive errors, cataract, glaucoma, and diabetic retinopathy, among others.[1] Of these conditions, glaucoma, associated with irreversible blindness, can be effectively managed when diagnosed early and treated appropriately, with ophthalmic drops forming part of the management strategy.[2]

Ophthalmic drops are sterile solutions or suspensions intended for topical administration into the eye. These formulations contain pharmacologically active agents such as antibiotics, mydriatics and anti-inflammatory drugs, and may also include antimicrobial preservatives as excipients to maintain microbial stability. There are many different routes of administration for pharmaceutical products, and the site of administration plays an important role in the effectiveness of medicine. The localised delivery of ophthalmic drops directly into the conjunctiva, eyelid epidermis, or cornea offers a targeted effect, making it advantageous in managing ocular conditions such as dry eye and glaucoma, as well as inflammatory conditions of the anterior segment.[3]

Despite the proven efficacy of ophthalmic drops in treating several ocular conditions, prognosis remains poor due to various contributing factors, such as patient nonadherence, perceived inconvenience, preference for oral medication, and improper administration techniques.[4] As a result, failure to correctly use ophthalmic drops may prolong these conditions, leading to permanent visual impairment.[5] Unaddressed visual impairment impacts health, social inclusion, and economic productivity, reducing educational opportunities and quality of life and increasing mortality risk.[6] Thus, reiterating the importance of early intervention and management.

Although ophthalmic drops are integral to therapeutic efficacy, studies have shown that many patients struggle to administer them appropriately.[7] Factors such as difficulty reading labels and improper administration technique can lead to misidentification of medication or the treated eye, reduced dosage, contamination, and ocular complications.[4] In addition, for ophthalmic drops to produce the required effect, they should be chemically and microbiologically stable, retaining their physical, chemical and microbial properties integrity, and microbial properties throughout their designated shelf life.[8] Exposure to high temperatures and humidity can cause instability; therefore, patient education on correct storage is vital in maintaining drug stability and preventing contamination.

Patient adherence refers to the extent to which patients' actions and behaviours align with physicians' instructions.[9] Poor compliance often results from a combination of factors including complex dosage regimes, physical barriers such as reduced manual dexterity or visual impairment as well as limited knowledge regarding ocular conditions and the importance of treatment adherence.[9] Within the framework of patient-centred care, improving compliance requires involving patients in their treatment plans and overcoming communication barriers that frequently arise between patients and healthcare providers. These barriers can adversely affect patient adherence when patients lack a complete understanding of their condition and the rationale behind the treatment intervention. Therefore, effective patient education is critical for improved compliance and treatment outcomes

Methodology

A scoping review, approved by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (Reference number: 00006097), was undertaken to explore this topic of interest. The objective of the review was to better understand patients' knowledge and awareness regarding the appropriate use and storage of ophthalmic drops.

Inclusion criteria

- All published research articles that explicitly defined knowledge and awareness of ophthalmic drop use.
- Studies that describe their sampling technique.
- Studies conducted and published between the years 2000 and 2020 were included to align with the timeframe of original project and data collection. Despite this cutoff, the included studies provide valuable insights into patient knowledge and awareness of ophthalmic drop use, which remain relevant to current clinical practice.
- Articles published in English.

Exclusion criteria

- Studies where the definitions of knowledge and awareness were not specified.
- Studies published prior to the year 2000.
- Grey literature.
- Articles in languages other than English.

PCC framework

The PCC (population, concept, context) framework was used to guide the selection of relevant studies:

- Population: Any population of any age group.
- Concept: Knowledge and awareness of ophthalmic drop usage and storage.
- Context: Peer-reviewed articles published between 2000 to 2020.

Search strategy and data synthesis

A comprehensive literature review search was conducted, retrieving articles from three electronic databases: Google Scholar, PubMed and Cochrane Library. The search strategy incorporated a combination of Medical Subject Headings (MeSH) and relevant keyword**s**, including:

- Eye drops, ophthalmic solutions, eye preparations, ophthalmic drops
- Instillation, administration, usage.
- Correct use, correct administration, correct instillation
- Eye drops knowledge, compliance on eye drop usage, adherence to eye drops

Data organisation and screening

- *Rayyan QCRI*, a web-based tool for systematic reviews, was used to detect duplicate records and to assist with the screening and selection of studies

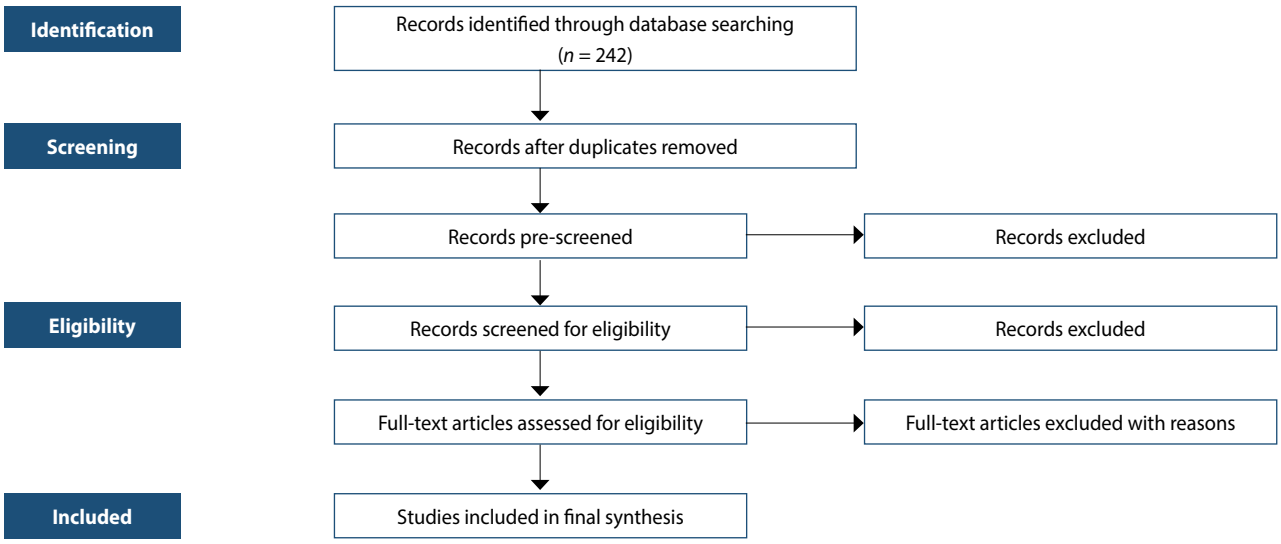

Figure 1: Flow diagram illustrating the selection process for inclusion of studies in the systematic review

- *Microsoft Excel* was employed to capture key article findings for analysis.

Data extracted from included studies

The following information was extracted from each eligible study:

- Author identifiers
- Year of publication
- Study location
- Study design
- Sample size
- Sampling technique
- Age of study participants
- Method used to assess knowledge
- Method used to evaluate awareness

Figure 1 provides a visual representation of the literature review conducted.

From an initial pool of 242 articles retrieved using MeSH terms related to eye drops and their administration, 212 were screened. After evaluating titles and abstracts, 92 full-text articles were assessed for eligibility. Of these, only 28 studies met the inclusion criteria and were included in the final analysis (Table I).

Results

Summary of key characteristics and findings of reviewed studies.

The included studies were conducted in clinical settings across multiple countries, with study sample sizes ranging from 26 to 5100 (mean ≈ 315). Study populations included glaucoma patients (14 studies), postoperative cataract patients (2), patients with both glaucoma and ocular hypertension (2), and individuals with other ocular conditions (10).

Techniques for assessing eyedrop instillation included video recordings (9 studies), questionnaires (10), both methods (5), and observation (4). Most studies employed a prospective cross-sectional design, with others including longitudinal and randomised components.

Discussion

This review aimed to assess patients' knowledge and awareness regarding the correct use and storage of ophthalmic drops. Inadequate instillation technique, irrespective of treatment experience and duration, was a recurring finding across several studies.[9,13-15,24,25,32] Common challenges identified included touching the bottle tip, missing the eye, and failing to wash hands prior to drop installation.[25,32] These behaviours increase the chances of contamination and reduce treatment efficacy. Furthermore, ocular conditions deteriorate due to poor eyedrop instillation.[17] Studies outlined various factors contributing to poor instillation, including a lack of knowledge about ophthalmic drops.

Several reviewed studies focused on glaucoma patients; however, long-term therapy did not guarantee proper technique, especially among older adults who face dexterity and visual impairments.[9,12,15,16] This suggests that familiarity with the procedure, compounded by other factors, affected competency. It was further noted that improper application may persist even after years of eyedrop use.[24]

Enhanced education and communication from healthcare providers was associated with improved technique.[26] However, deficits in patients' knowledge on areas such as handwashing and checking of expiry dates were noted, often due to lack of patient education.[22]

The majority of the studies used a combination of questionnaires and video recordings to assess patients' ability to administer ophthalmic drops. Video demonstrations were deemed valuable, providing an accurate assessment of patient instillation techniques and allowing gaps to be identified.[9,18,19,28,35] Video recordings further served as an instrument to enhance patient education. Several studies indicated that education and counselling improved instillation proficiency, highlighting the importance of patient education in reducing errors and minimising adverse effects, advocating for its inclusion in clinical settings.[11-14,18,24-26]

Given these findings, it is essential that healthcare providers not only counsel patients but also demonstrate proper instillation techniques and confirm patient understanding at the point of dispensing.[12,13,26,29] In addition, patients' lack of knowledge on how and where to store ophthalmic drops also emerged as a gap.[16] This is possibly due to insufficient counselling in this area, as administration may be prioritised over storage.

Recommendations

It is recommended that the following minimum information should be conveyed to patients to support and promote therapeutic outcomes: correct instillation technique (single drop, avoid contact with the eye or bottle tip), hand hygiene before administration, identifying the correct eye and timing of doses, checking expiry dates and discarding drops appropriately (28–30 days or per manufacturer guidelines), avoiding bottle contamination, proper storage conditions, and recognising adverse effects. Providing this information can improve patient compliance, reduce complications, and maximise the efficacy of ophthalmic therapy.

Limitations

This review is not without limitations. Eyedrop administration awareness was omitted from the search strategy, and this oversight may have affected the results. Most studies focused on glaucoma patients, limiting generalisability to other ocular conditions that use ophthalmic drops. This also highlights a notable gap in literature, at the time of this study, regarding the use, knowledge and difficulties associated with ophthalmic drops in diverse patient conditions. Furthermore, the majority of the reviewed

Table I: Key characteristics and findings of reviewed studies

Author(s)	Country and study location	Study design and type	Sample size and sampling method	Age and gender	Analysis method	Outcome measures	Results and conclusion	Limitations
Dietlein et al.[10]	Germany: Department of Ophthalmology, University of Cologne	Prospective, observational cross-sectional	44; consecutive sampling	80+ years; males and females	GraphPad Prism 2; Mann–Whitney and Spearman tests; significance set at $p < 0.05$	Patients self-administered eyedrops while being observed. Investigators recorded: ability to open the container, drop expulsion, contact with cornea/eyelid, and drops on lid/skin.	57% successfully instilled drops into the conjunctival sac (compared to 95% and 89% in control groups A and B). Container contact with the eye occurred in 68% of the study group. Challenges were linked to reduced visual acuity and lack of prior experience. *Conclusion*: Elderly patients struggle with self-administration from single-use containers.	Small sample size due to inclusion of only patients aged 80 and above.
Liu et al.[11]	Ghana: Crystal Eye Clinic, Accra	Prospective, nonrandomised control group, cross-sectional	218; selective sampling	19+ years; males and females	Video-recorded administration scored independently by two researchers; data analysed using ANOVA ($\alpha = 0.05$)	Proficient administration defined by: (1) drop touches and remains on ocular surface; (2) bottle tip does not contact eye or adnexa; (3) only one drop is applied.	84% of 133 educated patients achieved proficiency by day 30, compared to 59% of 49 in the non-educated group. Educated participants also reported reduced pain and irritation post cataract surgery. *Conclusion*: Patient education improves eyedrop instillation technique and post cataract surgical irritation.	Single-eye observation may not represent typical usage; observer presence could have influenced patient behaviour.
Naito et al.[12]	Japan: Sumitomo Besshi Hospital, Ehime Hospital, Yoshikawa Eye Clinic, Okayama Hospital	Prospective, observational, open-label, multicentre study	163; selective sampling	20+ years; males and females	*t*-test and Fisher's exact test for normally distributed variables; multivariable logistic regression for associations	Video-assessed success rate of eyedrop instillation in glaucoma patients and healthy volunteers; analysis of demographic and clinical predictors.	•Success rates: 38.5% in glaucoma patients, 56.5% in volunteers •Average attempts: 2.7 ± 1.4 (patients), 2.3 ± 0.7 (volunteers) • Bottle tip contact: 29.5% of patients, 15.3% of volunteers •≥ 2 attempts: 23.1% of patients, 20.0% of volunteers • Multiple drops in one attempt: 14.1% of patients, 8.2% of volunteers •Single drop flow into conjunctiva: 19.2% of patients, 3.5% of volunteers *Conclusion*: Glaucoma patients had poorer instillation technique compared to non-glaucoma volunteers, likely due to visual field impairment. These findings emphasise the importance of patient education in the affected population.	Only one bottle type was used and prior education on eyedrop instillation was not assessed.
An et al.[13]	Canada: Cataract clinics at General Justice Hospital	Prospective, consecutive, observational	54; selective sampling	18+ years; males and females	Odds ratios calculated using regression models	Post-surgery evaluation of patient eyedrop instillation technique via questionnaire and video recording on day one post-op.	• 22 patients (41%) waited ≥ 5 minutes between drops • **92.6%** (50 patients) demonstrated improper technique via video (e.g., missing the eye, incorrect drop count, bottle tip contamination, failure to wash hands) • Three patients (5.6%) instilled a stream of drops instead of a single drop •20 patients reported never missing the eye; however, 7 (35%) missed under observation, and 4 (57.1%) perceived their administration as correct •11 (39.3%) who believed they never touched their eye did so during observation Only 11 (30.6%) of 36 who reported always washing their hands, did so under observation *Conclusion*: Self-reported compliance with proper instillation technique often contradicted observed behaviour, emphasising the need for education.	• Small sample size • A single postoperative observation session may not reflect long-term behaviour

Gao et al.[14]	China	Observational; cross-sectional	113; selective sampling	18+ years; males and females	Regression analysis, means and standard deviations	Demographic and clinical data of glaucoma patients were collected. Video recordings were used to assess adherence to proper eyedrop instillation technique.	• 93.8% of patients maintained a > 5-minute interval between drops while 3.5% pressed the nasolacrimal duct post-instillation • 48.7% correctly instilled eyedrops on first attempt • Average drops used: 1.7 ± 0.8 • Of those correct on first try: 46% missed the eye, 7% touched the bottle tip to the conjunctiva or cornea and 24% touched eyelids or lashes • Only 9.7% had prior education on proper eyedrop instillation, primarily from doctors or nurses. *Conclusion:* Poor eyedrop administration of glaucoma patients in China.	•Observer presence may have influenced patient behaviour. •Administration was assessed in only one eye; however, glaucoma treatment is typically instilled bilaterally.
Virani et al.[15]	India: Primary Health Care centre	Interventional, prospective	69; selective sampling	18–80 years; males and females	*t*-test, multivariable regression; means and standard deviations	Questionnaire-based assessment of instillation difficulties. Patients received assistance for 4 weeks, and thereafter, the effectiveness of the intervention was measured by IOP reduction.	•87% of patients instilled ophthalmic drops bilaterally and 13% in one eye •29 patients reported subjective difficulties, with 26 reporting multiple challenges such as bottle tip contact, identifying drops, capping, extra drops, and multiple instillation •Difficulties were more prevalent in patients over 60 •After 4 weeks of assistance: IOP decreased significantly by 1.61 mmHg (right eye) and 1.92 mmHg (left eye) •Average bottle use decreased by 0.35 per person with a 16% cost saving *Conclusion:* Patients above 60 years experienced challenges with eyedrop instillation, supporting the need for targeted intervention in geriatrics.	Small sample size and 12% dropout rate
Tsai et al.[16]	Baltimore and Fortworth	Quantitative pilot; cross-sectional	213; selective sampling	18+; males and females	Means, standard deviations	A two-page questionnaire was used to collect demographic data and assess knowledge, experiences, and challenges related to eyedrop use.	•Majority (82.6%) reported self-administered eyedrops, while •17.4% relied on others due to vision issues (25%), manual dexterity problems (25%), or difficulty dispensing a single drop (25%) • Those who self-administered mainly did so while sitting (37.8%) or standing (36.4%), often in the bedroom or bathroom without a mirror • Only 36.4% always washed their hands before use and 5% reported touching the dropper tip to the eye. • Most used both hands and 11.2% disliked applying drops •45.4% stored eyedrops in the bedroom, 23.9% in the bathroom, 19% in the kitchen, and 12.2% in the refrigerator *Conclusion:* The importance of patient education and follow-up visits was highlighted to ensure proper eyedrop administration.	Results relied on patients' honesty in response to the questionnaire.
Hennessey et al.[17]	United States of America: Private subspecialty retina /glaucoma practice	Prospective, observational, cross-sectional	409; consecutive sampling	>18 years; males and females	Multivariate logistic regression.	Patients completed a questionnaire, received 5mL of artificial tears to instil and were observed via recordings.	•Approximately one-third of both groups failed to place a drop on the ocular surface. • Retina patients used multiple drops, touched the eye more frequently, and made more attempts than glaucoma patients, who were slightly more successful at instilling a single drop. •Despite 80% of participants reporting no difficulty, 29-35% missed their eye. *Conclusion:* Correct eyedrop technique is crucial, and physicians should regularly counsel patients. The study demonstrated that poor instillation techniques occur even among experienced patients.	•Results may be influenced by the study's prospective design •Possible self-reporting bias, particularly among patients with poor vision, who had questionnaires read to them. •Variation in visual impairment levels was not accounted for in the analysis.

Choy et al.[18]	Hong Kong: Ophthalmology clinic of Queen Mary Hospital and Grantham Hospital	Prospective; cross-sectional	26 participants	> 60 years; males and females	•Prism GraphPad and SPSS reported frequencies, percentages, means and SDs •Paired *t*-tests, Spearman, and point-biserial correlations •Multiple linear regression to assess relationships between demographics and instillation ability	To identify risk factors for poor eyedrop technique and assess the benefits of patient education.	•Post-education score: 7.33 ± 1.27, showing a mean improvement of 1.90 ± 2.01 •FRAIL score was a significant predictor of technique (B = -1.087, $p = 0.003$), even after adjusting for age, sex, education, and cognitive function •Females had lower baseline scores (r = -0.402) but improved significantly after education (r = 0.392). *Conclusion:* Patients with poor functional status are at greater risk for poor instillation technique. However, structured education improved technique, thereby reducing contamination, wastage and maximising drug efficiency and adherence.	•As a prospective, self-controlled study, differences in demographics and questionnaire responses may affect data comparability. •Small sample size limits generalisability.
Lampert et al.[19]	Germany: community pharmacies	Cluster-randomised; cross-sectional	91 participants	>18 years; males and females	•Computer-generated randomisation •Before–after comparisons: McNemar tests •IBM SPSS Statistics V24	The effect of motivational education on long-term eyedrop administration.	Correct administration improved over time: 6% at baseline, 35% at one month and 64% at 6 months. Education methods included demonstrations, verbal and written counselling. *Conclusion:* Patient education, regardless of the mode of delivery, resulted in improved eyedrop technique, emphasising the need for consistent, reinforced practices.	•Small sample size • High dropout rate due to long follow-up period • Potential selection bias from cluster-randomisation •Use of placebo eyedrops differing from individual medications •Unassessed indications for eyedrop use.
Gomes et al.[20]	Brazil: Hospital Federal de Bonsucesso, Rio de Janeiro	Cross-sectional	71; consecutive sampling	55–77 years; both males and females	•JMP, v12.0 (SAS Institute) •Percentages, means and standard deviations	Observation parameters included: time to first drop after uncapping, number of drops squeezed, drop location, tip contact, whether the bottle was shaken, prior handwashing, eyelid closure ≥ 1 minute post-instillation and punctum occlusion after instillation.	•Only 28% of patients correctly instilled eyedrops without tip contact •62% had bottle contact, 49% had drops land on eyelids or cheeks, 27% squeezed multiple drops • Only 11% washed hands prior •Slightly better performance noted in females and younger age was significantly associated with correct technique (mean 61.2 vs. 68 years, $p = 0.02$). *Conclusion:* The majority of glaucoma patients struggled with correct eyedrop instillation, with younger age being the only significant factor associated with correct administration.	• Patients with motor impairments and severe visual loss (worse than hand movements) were excluded •Drop instillation history relied on patient recall •Eyedrop use was only observed once in a different setting, potentially affecting natural behaviour.
McVeigh and Vakros[21]	United Kingdom: Bath Royal United Hospital	Prospective, pilot	25; purposive sampling	45–90 years; both males and females	Bath Royal United Hospital, Bath	Evaluated the effectiveness of an educational drop chart (EDC) distributed with an information leaflet and two questionnaires (before and 1-month post-EDC use).	•Significant improvements noted in nine of eleven categories • Hand washing increased from 64% to 92% ($p = 0.029$), shaking the bottle from 40% to 84% ($p = 0.001$), and punctal occlusion from 44% to 72% ($p = 0.015$) •Discarding the bottle after 28 days rose from 68% to 92%, although not statistically significant ($p = 0.09$). *Conclusion:* EDC as a promising, cost-effective tool in improving use of topical ocular medications.	Small sample size and subjectivity
Mohindroo et al.[22]	India: Department of Ophthalmology, Government Medical College and Hospital, Chandigarh	Cross-sectional; quantitative	101; consecutive sampling	18-87 years; both males and females	IBM SPSS statistical software v21	The knowledge, attitude and practices of eyedrops instillation.	•98% knew the purpose of the medicine but only 61.4% knew appropriate storage practices •Nearly 30% believed two eyedrops could be instilled consecutively and 55.4% did not consider missing a dose significant. *Conclusion:* Variation in basic practices, such as handwashing and checking expiry dates before using eyedrops, indicates the need for education.	Lack of reviewing clinical charts

Ribeiro et al.[23]	Brazil: Instituto de Olhos de Maceió, Alagoas	Cross-sectional; quantitative	237 participants	Males and females	Chi-square test, $p \leq 0.05$	Questionnaire divided into three parts: demographics, glaucoma details, number of eyedrops used, education and self-rated vision • Morisky Adherence Scale (MMAS-8 • Adherence behaviours using a 5-point Likert scale	•Adherence to glaucoma drops was 54% •Age and number of drops ($p = 0.02$ and 0.03 respectively) and vision quality ($p < 0,001$) significantly influenced inappropriate use •Forgetfulness was the most common reason in both adherent (23%) and non-adherent (76.15%) groups. *Conclusion:* Over half of patients were non-adherent, forgetfulness and visual limitations were key contributing factors.	Excluded patients who missed appointments in the last 3 months and those not enrolled in the Glaucoma Project.
Alfawzan et al.[24]	Saudi Arabia: Buraidah Central Hospital	Prospective, cross-sectional	643; randomly selected	18–35 years, both males and females	SPSS software; Chi-square test $p \leq 0.05$	The questionnaire had three sections: demographics, eyedrop administration and storage behaviours, and the role of pharmacists in improving compliance.	•Majority (82.5%) avoided bottle tip contact and 90.8% applied ointment after eyedrops, while 30.6% allowed less than 5 minutes between treatments. 30.5% waited 5–10 minutes. • 32.5 % reported always washing their hands before instillation, with 29.6% washing occasionally. *Conclusion*: All patients reporting incorrect eyedrop use indicated the need for counselling to ensure effective treatment.	•Observation was not done to verify self-reported data •Inclusion extended to only individuals who had access to social networking, which may not affect the broader population.
Gupta et al.[25]	India: Tertiary eye care facility	Observational; cross-sectional	70 participants	35–70 years	Means and standard deviations	Patients' ability to instil a single eyedrop at home, the time taken, accuracy and container contamination were evaluated.	• 63% had primary angle-closure and 37% primary open-angle glaucoma •Mean time to instil the first drop ranged from 8.7 to 23.5 seconds. •Only ~50% could squeeze a single drop, and 53 patients touched the bottle tip to the eye or eyelids, risking contamination • Drops missed the eye in 22 patients, with some misdirecting multiple drops • Only 6 patients correctly instilled a single drop into the conjunctival sac. *Conclusion*: Overall, 90% failed to instil drops properly, emphasising the need for education to improve adherence to medication.	•Socioeconomic status and literacy levels were not assessed. •Patients with physical impediments were excluded.
Tatham et al.[26]	United Kingdom: University Hospital Leicester	Observational; cross-sectional	85 participants	50–90 years	•Means and standard deviations at different time points •Histograms: Shapiro-Wilk test •Wilcoxon rank-sum test •Univariable logistic regression	The outcome was scored from 1 (worst) to 4 (best), based on the patient's ability to instil a single eyedrop.	• The average patient age was 71.6 ± 11.6 years. •65.7% had poor technique (scores 1–2), including missed eyes, touching the bottle tip contact. • 81.2% recalled being shown how to instil drops by an ophthalmic professional. •Patients taking two or more medications often instil drops without appropriate intervals •Difficulty ratings varied with 34 patients rating difficulty 1/10, 18 rated 2/10 and 13 3/10. Only 9 patients rated eyedrop difficulty a 5. •No significant differences were found based on gender, ethnicity, education, or visual acuity. Age was strongly linked to poorer instillation technique. *Conclusion:* There was a clear relationship between patient education and correct eyedrop instillation. Education should be a routine part of glaucoma care.	•Potential patient recall bias. •Clinic setting and observation may have altered patient behaviour. •Handedness was not assessed, which could impact technique. •The role of compliance aids was not evaluated, which could support instillation accuracy.

Sakiyalak et al.[27]	Thailand: Faculty of Medicine, Sariraj Hospital, Mahidol University	Cross-over design, randomised	59 participants	> 18 years; both males and females	•Means, standard deviations at different time points • *p*-values •Eyedrop guide •Univariate and multivariate analysis of risk factors for instillation failure, summarised with EDGs	Patient's instillation ability, time taken, technique used, amount of drug delivered, and spillages were assessed via video recording	•Out of 64 glaucoma patients, 26 (40.6%) succeeded in eyedrop instillation with their usual technique •Five withdrew before the week 2 visit, therefore 59 participants completed the study •Success rates were 61% for EDG and 66.1% for traditional techniques, with no significant difference •The number of patients unable to instil 1 drop using the EDG technique was almost double than that of the traditional method •13 participants contaminated the bottle using the traditional method •The EDG method took longer to instil drops. *Conclusion:* No correlation between adherence and demographics, clinical factors, or glaucoma knowledge, suggesting that personalised strategies are needed to improve adherence.	•High expectations of EDG may have increased false positives and reduced statistical power. •Single session video observation may not reflect routine behaviour. •Investigator presence might have influenced patient comfort and instillation performance. •No baseline data to verify consistency.
Feng et al.[28]	United States of America: Ophthalmology clinics at the University of Minnesota.	Prospective; cross-sectional	34; selective sampling	19–91 years; males and females	•Chi-square. •Pearson's *t*-test	Assess the effectiveness of patient education using a handout and instructional video on eyedrop self-administration.	•Before teaching, 47% had never been instructed on proper eyedrop administration, among them 88% felt confident while 12% did not • 9% always worried about missing a dose, 3% often and 56% sometimes worried •Post-teaching, 91% felt confident and 94% correctly pulled down their lower eyelid (increase from 47%) •More patients correctly instilled drops (91% vs. 59%), and behaviours like eyelid closure, digital pressure and avoiding surface contact improved after education. *Conclusion*: Post instructional videos, patients showed improvement in eyedrop instillation, viewing the materials as helpful. Thus, warranting inclusion in counselling, especially for OTC drops to reduce misuse, wastage, contamination and ocular injury.	•Short study duration limits long-term retention assessment. Future research should evaluate technique retention over time and reinforce education during follow-up. •Small sample size
Saynera et al.[29]	United States of America: Ophthalmology clinics in 4 states	Prospective; cross-sectional	279; selective sampling	> 18 years; males and females	IBM SPSS Statistics v19 with statistical significance at $p < 0.05$.	Role of communication and patient confidence/ self-efficacy in eyedrop use	• Only 40 patients received education on eyedrop use from ophthalmologists •Higher education levels improved accuracy while women frequently touched the applicator to their eyes or face •Severe glaucoma, female gender and low health literacy were significantly linked to poor technique •Mobility impediments adversely affected accuracy •African American patients were significantly less likely to contaminate the applicator. *Conclusion*: Significant associations noted between gender, glaucoma severity, and question-asking with poor eyedrop technique. Physicians should encourage patient questions and demonstrate eyedrop instillation. Further research is needed on effective educational tools.	•Possible selection bias as reasons for non-participation was not tracked. • Limited racial diversity as most non-African American patients were white. •Camera issues affected the clarity of some video evaluations. • Bottle variations (Systane) may have influenced technique. •Performance anxiety during observation could have affected results. •Prior instruction on eyedrop use was not assessed.

Curtis et al.[9]	Australia: Sydney Eye Hospital	Cross-sectional	100; selective sampling	18–90 years; males and females	•Responses were analysed as "yes/no" or "correct/incorrect", • Chi-squared tests	Evaluate patients' knowledge and behaviours with glaucoma eyedrop therapy and the impact of interpreters or English-speaking family members on patients' understanding and compliance.	•77% knew the eyedrop names, with non-English speakers less informed • 88% indicated receiving clear instructions •13 patients reported difficulties with instillation •Only 49% knew to close their eyes post-instillation •46% missed doses, and 8 had discontinued treatment without medical advice. *Conclusion*: Missed doses occurred regardless of demographics. Interpreter use did not significantly influence adherence. Older patients and those on long-term therapy had poorer knowledge, indicating a need for ongoing education by nurses.	•Only glaucoma patients included. •Technique was not observed, preventing assessment of instillation practices.
Stone et al.[30]	United States of America	Cross-sectional	139; selective sampling	> 18; males and females	•Video review of technique •Medical record review •Commercial analysis software.	Evaluate eyedrop instillation of experienced patients with ocular hypertension and glaucoma.	•92.8% reported no difficulties with eyedrop administration, and 61.9% believed they never missed the eye •79.2% reported no bottle tip contact •61.9% reported prior handwashing; however, observation showed only 1.7% washed hands •Among those using 15-mL and 2.5-mL bottles, 21.9% and 30.8%, respectively, instilled a single drop without touching the eye. *Conclusion:* Experienced patients demonstrated poor technique in instilling a single drop without bottle tip contact, indicating a discrepancy between self-reported data and practices.	•Only glaucoma patients included. •41 videos from 34 patients were lost due to a technical error.
Kawai-Tsuboi et al.[31]	Japan Nayoro City General Hospital	Retrospective; cross-sectional	67; consecutive sampling	52–95 years; males and females	•Humphrey field analyser •Means and standard deviation •Logistic regression analysis	Evaluate eyedrop administration methods (aided or unaided), the number of drops per instillation; placement accuracy, weekly usage frequency and awareness of local side effects.	•Inaccurate eyedrop placement accuracy was significantly associated with more bottles prescribed monthly ($p = 0.008$) •Patients using ≥ 2 drops per application also received more bottles, with the number of drops per instillation ($p = 0.029$) influencing prescription quantity. *Conclusion:* Prescription patterns correlated with instillation technique (i.e., accuracy and drop usage), but no significant links were found between technique and demographic variables.	•Small sample size and retrospective design. •Reliance on self-reported data potentially overestimated use and may not accurately reflect patient behaviour.
Park et al.[32]	United States of America: Chicago, Philadelphia, Tucson, AZ, Rochester.	Prospective; cross-sectional	78; consecutive sampling	40–85 years; males and females	•Kappa statistics •3 masked graders •Means	Video recordings of self-instilling artificial tears assessed efficacy (drop on ocular surface), safety (bottle tip contact) and efficiency (drops expressed).	•Efficacy: 79.5–87.2% (right eye), 74.4–87.2% (left eye). •Safety: 46.2–66.7% (right eye), 57.3–74.4% (left eye) made no contact with the eye •Efficiency: 64.1–76.9% (right eye), 64.1–89.7% (left eye) used one drop per instillation. *Conclusion:* Overall, 23 of 78 patients touched the bottle tip, indicating poor safety practices and a lack of knowledge that could possibly negatively affect long-term adherence.	•Use of a artificial tear bottle than patients' glaucoma medication bottles. •Some videos were blurry or incomplete, limiting accurate assessment. •Kappa statistics possibly underestimated the actual assessment between graders.
Tsumura et al.[33]	Japan: Hospitals and Clinics of Ophthalmologists Association	Prospective; longitudinal	5100; purposive sampling	+20 years; males and females	•Logistic regression •MD of Humphrey visual field analyser •Means ± standard deviations	Assess difficulty awareness, instillation intervals, recent forgetfulness and timings, assistance, use of aids, preferred number of drops and preferred frequency of instillation.	•Good adherence was reported by 72.4% of subjects and 78.5% of ophthalmologists •Missed instillations commonly occurred at noon (48.2%), before sleep (20.5%), evening (15.8%), and morning (14.0%). *Conclusion*: Longer treatment duration, age, and the number of drops per instillation negatively affected adherence. Females showed significantly better adherence than males.	Participants were pre-selected to use fixed combination drops, introducing selection bias.

Welge-Lussen et al.[34]	Germany: University Eye Clinic, Friedrich-Alexander University, Erlangen	Prospective; cross-sectional	123; consecutive sampling	45–88 years; males and females	•Means, standard deviations at time points T1 and T2. •Bivariant correlations •Regression models	Knowledge and self-reported adherence assessed using ARMS2 and VAS-AD	•18.5% of patients always took drops correctly according to VAS-AD. •77.9% missed no doses in the prior 14 days •Forgetfulness (43.8%) was the main reason for nonadherence, followed by inattentiveness (25%). •One third of patients missed doses when applying more than once daily. *Conclusion:* No link was found between adherence and demographic, clinical characteristics, or glaucoma knowledge data. Individualised strategies are recommended to improve adherence.	•Potential social desirability bias in self-reports. •Small sample size. •Short interval between T1 and T2. •Lack of data on environmental, social, and medication factors. •No control group was included.
Lazcano-Gomez et al.[35]	Mexico: Prevent Blindness Association (APEC Hospital de la Ceguera)	Prospective; cross-sectional	45; consecutive sampling	25–86; males and females	•SPSS software •Means, standard deviation and percentages	Patients on glaucoma treatment for ≥ 6 months were video-recorded instilling eyedrops, educated on proper technique, and reassessed post-education.	•Before education, patients squeezed 1.9±0.9 drops (0.9±0.7 reached the eye), with 64.4% touching ocular tissues, 61% had bottle tip contact and 66.7% instilled one drop •Post education, patients squeezed 1.2±0.5 drops (1.2±0.4 reached the eye), with 82% instilling one drop. *Conclusion:* A single educational session improved both the efficiency and accuracy of instillation.	•Small sample size. •Brief follow-up (only 30 minutes post-education) limiting understanding of long-term retention and technique.
Hein et al.[36]	United States of America: Duke Eye Centre and the Durham VA Medical Centre	Prospective cohort; cross-sectional	137; consecutive sampling	Not specified	SAS 9.4	Patients rated their confidence in eyedrop instillation, followed by observing the administration.	•Among 117 confident participants, only 95 used the correct technique •Of 18 not confident, 11 used the correct technique •Overall, 78% demonstrated correct eyedrop instillation. *Conclusion*: Self-reports and confidence levels do not confirm correct installation; therefore, direct observation is necessary.	The confidence question was vague and may have led to misinterpretation, failing to reflect patient ability accurately.

studies were conducted in developed countries with higher literacy levels, which may not accurately reflect the difficulties faced in developing countries. In addition, most studies examined eyedrop instillation with limited focus on storage practices. Only one study specifically addressed both knowledge of eyedrop usage and storage, highlighting the scarcity of evidence in this area. Consequently, eyedrop storage practices are relatively understudied, and their impact on treatment outcomes remains unclear, representing an important knowledge gap that warrants further investigation.

Conclusion

This literature review confirmed that patients lack sufficient knowledge on eyedrop administration, while evidence regarding storage practices is limited. Where available, gaps were noted in essential practices such as handwashing, checking of expiry dates, discarding drops after 28–30 days depending on manufacturer guidelines, avoiding bottle contamination, and accurate instillation of a single drop. Poorly executed eye-drop instillation techniques adversely affected treatment adherence. An evident gap exists between patient education and knowledge on proper administration, warranting improvement in healthcare communication and information dissemination in clinical settings. Strengthening patient education is critical for achieving proficiency and ensuring safe practices necessary for compliance and treatment efficiency.

Conflict of interest

The authors declare no conflict of interest.

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Ethical approval

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ORCID

D van Staden https://orcid.org/0000-0003-2028-1711

S Gopaul https://orcid.org/0009-0006-8554-6855

References

1. Bourne RRA, Flaxman SR, Braithwaite T, et al. Magnitude, temporal trends, and projections of the global prevalence of blindness and distance and near vision impairment: A systematic review and meta-analysis. Lancet Glob Health. 2017;5(9):e888-97. https://doi.org/10.1016/S2214-109X(17)30293-0.
2. Rawlins EA. Bentley's textbook of pharmaceutics. 1st ed. India: Laxman Chand Arya for All India Traveler Bookseller; 1992. p. 358.
3. Terry JE. Ocular disease detection, diagnosis, and treatment. Stoneham: Butterworth Publishers; 1984. p. 13. https://doi.org/10.1097/00006324-198412000-00008.
4. Sleath B, Byrd JE, Robin AL, Covert D, Tudor G. Glaucoma patient receipt of information and instruction on how to use their eye drops. Int J Pharm Pract. 2008;16:35-40. https://doi.org/10.1211/ijpp.16.1.0007.
5. Shaw M. How to administer eye drops and eye ointment. Nurs Stand. 2016;30(39):34-6. https://doi.org/10.7748/ns.30.39.34.s42.
6. Jones N, Bartlett HE, Cooke R. An analysis of the impact of visual impairment on activities of daily living and vision-related quality of life in a visually impaired adult population. Br J

Full list of references available on request

Clinical management of hirsutism: An integrated approach

RM Moosa-Battey, KC Mbara

Department of Pharmaceutical Sciences, Tshwane University of Technology, South Africa

Corresponding author, email: batteyrm@tut.ac.za

Abstract

Hirsutism, the excessive growth of coarse terminal hair in women in a male-pattern distribution, is a common condition with multifactorial aetiology and substantial psychosocial impact. Affecting 5–15% of women of reproductive age, it is most often linked to polycystic ovary syndrome (PCOS), idiopathic hirsutism, or, less commonly, non-classic congenital adrenal hyperplasia, androgen-secreting tumours, and drug-induced causes. Effective management requires a comprehensive approach, beginning with accurate diagnosis through clinical scoring systems, laboratory investigations, and imaging, where indicated. Treatment is typically multimodal, combining lifestyle modification, cosmetic and mechanical hair removal, physical methods such as laser therapy and electrolysis, and pharmacological options including combined oral contraceptives, antiandrogens, insulin sensitisers, and topical agents like eflornithine. Adjunctive use of herbal and emerging therapies shows promise but requires further validation. Given the chronic nature of hirsutism, ongoing treatment and counselling are critical to improving quality of life and addressing associated psychosocial burdens. An integrated, patient-centred approach that considers both physical and psychological outcomes remains central to effective long-term management.

Keywords: Hirsutism, polycystic ovary syndrome, hyperandrogenism, antiandrogen therapy, laser hair removal, psychosocial impact

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Introduction

Hirsutism, defined as the excessive growth of coarse, terminal hair in women in a male-pattern distribution (e.g., face, chest, abdomen, back, upper arms, thighs), is a common and distressing clinical condition.[1] It affects approximately 5% to 15% of reproductive-aged women globally, with higher prevalence rates noted in certain ethnic groups, including Mediterranean, Middle Eastern, and South Asian populations.[1] While often viewed as a cosmetic concern, hirsutism can significantly impact a woman's psychosocial well-being, self-esteem, confidence, and daily functioning, leading to emotional distress, social embarrassment, anxiety, and even depression.[1] This review article synthesises current understanding of the aetiology, diagnosis, and comprehensive management strategies for hirsutism. While specific, large-scale, national epidemiological studies solely on hirsutism in South Africa are limited, it is closely linked to polycystic ovary syndrome (PCOS), which is highly prevalent in the country.

Aetiology and pathophysiology

Hirsutism is primarily a sign of underlying hyperandrogenism, resulting from either increased androgen production, enhanced peripheral metabolism of androgens (especially testosterone conversion to dihydrotestosterone (DHT) by 5α-reductase), or increased sensitivity of hair follicles to androgens. Androgens play a crucial role in transforming fine vellus hair into coarser terminal hair, particularly in androgen-sensitive areas.[1,2]

Key causes: Most cases of hirsutism are due to functional causes of excess androgens, with the majority falling into a few common categories.[3]

Polycystic Ovary Syndrome (PCOS)

This is the most prevalent cause, accounting for over 70% of hirsutism cases. PCOS is characterised by at least two of the following: chronic anovulation, clinical or biochemical hyperandrogenism, and polycystic ovaries. Hyperinsulinemia, common in PCOS, triggers increased ovarian and adrenal androgen production and decreased sex hormone-binding globulin (SHBG) synthesis, leading to higher levels of biologically active free testosterone.

Idiopathic hirsutism

Diagnosed by exclusion, this refers to hirsutism in women with normal ovulatory menstrual cycles and normal androgen concentrations. It is suggested to be due to exaggerated peripheral 5α-reductase activity, altered androgen metabolism, or androgen receptor polymorphisms. This accounts for approximately 5–20% of cases.[3]

Non-classic congenital adrenal hyperplasia (NC-CAH)

An autosomal recessive disorder, NC-CAH results from a partial deficiency of enzymes (most commonly 21-hydroxylase) involved in cortisol production, leading to androgen precursor shunting into the androgen pathway. Its clinical presentation often mimics PCOS.[3] Approximately 50–70% of women with NC-CAH develop hirsutism (increasing from adolescence into adulthood).

Androgen-secreting tumours

These are rare (0.2% of hirsutism cases) but serious causes, presenting with rapid-onset hirsutism, virilisation (e.g., clitoromegaly, deepening voice, increased muscle bulk, male

pattern baldness, breast atrophy), or a palpable abdominal/pelvic mass. Over 50% of these tumours are malignant.[4]

Drug-induced hirsutism (non-androgenic hirsutism)

Certain medications, such as anabolic steroids, danazol, cyclosporine, diazoxide, glucocorticoids, minoxidil, phenytoin, and valproic acid, can cause hirsutism or hypertrichosis. Hair growth typically resolves upon discontinuation of the causative agent.[4]

Other endocrine disorders

Hyperprolactinemia, thyroid disorders, and acromegaly are less common causes of isolated hirsutism. Hyperprolactinemia has been linked to increased dehydroepiandrosterone (DHEA) and DHEA sulphate (DHEA-S) levels and can lower SHBG, thereby raising free testosterone concentrations.[4]

Psychosocial and financial impact

Hirsutism is not merely a physical condition; it carries a substantial psychosocial and financial burden.[4] Women with excessive facial hair report negative self-perception, emotional instability, limited social interaction, and significant distress.[5] The mean Dermatology Life Quality Index (DLQI) score in hirsute females suggests a "very large" psychosocial impact.[5] Patients may experience feelings of shame, inferiority, rejection, anxiety, and depression.[6] The time, energy, and funds spent on hair removal contribute to a considerable financial burden. For example, laser therapy, despite its effectiveness in achieving long-lasting hair reduction for hirsutism, has huge cost implications, which can be prohibitive for many patients.[6] This encompasses not only the cost of the treatment itself but also the multiple sessions typically required to achieve the desired treatment outcomes.[6]

Diagnosis and assessment

A comprehensive approach that includes a detailed history and physical examination, along with targeted laboratory investigations, is essential for diagnosing hirsutism and identifying its underlying cause.

Clinical assessment

Modified Ferriman-Gallwey (mFG) score

This visual scoring system quantifies hirsutism by evaluating hair growth in nine androgen-sensitive body areas (upper lip, chin, chest, upper back, lower back, upper abdomen, lower abdomen, upper arms, and thighs), with scores from 0 (no terminal hair) to 4 (extensive terminal hair) for each area, yielding a total score up to 36.[3,6,7]

Ethnic variations

Cut-off scores for defining hirsutism vary significantly by racial and ethnic background.[7] For instance, a score of ≥ 8 is considered hirsutism in British and United States black and white women, while it is ≥ 9 in Mediterranean, Hispanic, and Middle Eastern women, ≥ 6 in South American women, and as low as ≥ 2 for Han Chinese women. Scores of 3–15 indicate mild hirsutism, 16–25 moderate, and > 25 severe.[7]

History taking

Key aspects include age of onset, progression speed, menstrual history, fertility, weight changes, family history of hyperandrogenism, current medications, and previous hair removal treatments.[6] Rapid onset or progression, especially with signs of virilisation, suggests an androgen-secreting tumour.[6]

Physical examination

This involves assessing hair type (vellus vs. terminal) and distribution to differentiate hirsutism from hypertrichosis.[6] Examination should also include anthropometric measurements (BMI, waist circumference, blood pressure) and a skin assessment for acne, striae, acanthosis nigricans, or signs of virilisation (e.g., clitoromegaly, deepening voice, male pattern baldness, breast atrophy, increased muscle mass).[6]

Laboratory investigations

Androgen levels

Testing for elevated androgen levels is recommended for women with moderate to severe hirsutism, or any degree of hirsutism if it is sudden in onset, rapidly progressive, or associated with menstrual irregularity, central obesity, or clitoromegaly.[6] Routine testing is often not needed for mild hirsutism with regular menses. Total testosterone and SHBG levels should be measured, ideally during the early follicular phase. Free testosterone is the biologically active component, but its measurement requires accurate methods like equilibrium dialysis. High testosterone levels (> 200 ng/dL) are highly suggestive of adrenal or ovarian tumours.[6]

Other hormones

- DHEA-S: Elevated levels suggest an adrenal origin.
- 17-Hydroxyprogesterone (17-OHP): Routinely performed for hyperandrogenic hirsutism to screen for NC-CAH.[7]
- Prolactin and TSH: To rule out hyperprolactinemia and thyroid dysfunction, especially in patients with amenorrhea or other consistent symptoms.[7]

Imaging

Transvaginal ultrasonography for suspected ovarian masses (e.g., PCOS, tumours) and CT/MRI of the abdomen or pelvis for suspected adrenal masses. Pituitary imaging may be needed for hyperprolactinemia.[7]

Treatment modalities

Effective treatment for hirsutism often involves a multimodal approach combining physical hair removal techniques with medical therapies (Figure 1). Patients should be informed that hirsutism is a chronic condition, and recurrence is likely if treatment is discontinued. Due to the hair growth cycle, pharmacological

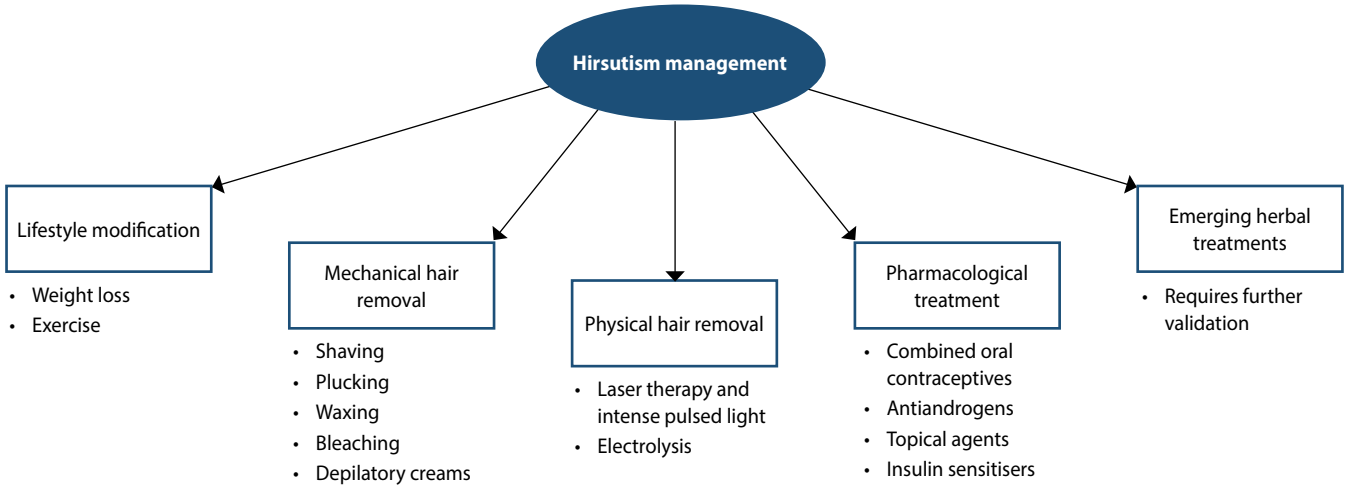

Figure 1: Multimodal approaches for management of hirsutism. Different modalities, including lifestyle modification, cosmetic and mechanical hair removal, physical methods such as laser therapy and electrolysis, and pharmacological options, are often used in combination to manage hirsutism

treatment effects typically manifest after several months (e.g., 6 months for facial hair).[8]

Lifestyle interventions

Weight loss and exercise

For overweight and obese women, especially those with PCOS, lifestyle changes (diet, exercise) can significantly reduce insulin resistance, lower androgen production, increase SHBG, and improve hirsutism scores.[8,9]

Shaving, plucking, waxing, bleaching, depilatory creams

These provide temporary relief but do not affect hair growth or thickness.[10]

Laser therapy and intense pulsed light (IPL)

These technologies target melanin in hair follicles, inducing thermal coagulation.

- *Types:* Long pulse alexandrite, Nd: YAG, diode lasers, and IPL are commonly used.[11]
- *Efficacy:* Laser therapy offers semi-permanent hair removal and is among the most common dermatologic procedures. Studies show 60–75% hair reduction after 4–8 IPL sessions, though complete clearance is rare. Alexandrite laser can achieve up to 80% hair reduction, with ~95% efficacy on axilla and ~75% on upper lip, usually requiring around five sessions.[11,12]
- *Limitations:* Less effective for light/white hair due to lack of melanin, requires multiple sessions, and carries risks of pain, dyspigmentation, and scarring. Most effective for dark hair on fair skin; Fitzpatrick type VI often excluded due to risk of post-inflammatory hyperpigmentation.[12]

Electrolysis

The only FDA-approved permanent hair removal treatment, involving destruction of individual hair follicles with an electric current. Effective for all hair and skin types, though time-consuming.[9] Its main limitations are time, cost, pain, and practicality for large areas, making it best suited for targeted treatment rather than extensive hirsutism.[9]

Pharmacological treatments

Pharmacological therapies aim to suppress androgen production or block androgen receptors and are often the first-line medical approach, particularly for women not trying to conceive (Table I).[1-18]

Emerging herbal treatments

Research is exploring natural alternatives due to potential side effects of conventional drugs (Table II).[1-20]

Role of the pharmacist

Pharmacists play a crucial role in the multidisciplinary management of hirsutism by combining their expertise in medicines with patient-centred care. They are often the first point of contact for women seeking advice and can provide education on the underlying causes of hirsutism such as polycystic ovary syndrome (PCOS), adrenal hyperplasia, or idiopathic presentations.[7] Pharmacists counsel patients on the available pharmacological options, including combined oral contraceptives, antiandrogens like spironolactone or cyproterone acetate, topical eflornithine, and insulin sensitisers, ensuring that patients understand how these therapies work, their expected timelines for effect (usually 3–6 months), and possible side effects such as venous thromboembolism risk with COCs or hyperkalaemia with spironolactone.[8] They emphasise the importance of adherence, discuss the need for reliable contraception when using teratogenic antiandrogens, and monitor for drug interactions or contraindications. Beyond pharmacotherapy, pharmacists also provide guidance on lifestyle modification – such as diet, exercise, and weight management – which is particularly important in PCOS-related hirsutism, and they help patients navigate adjunctive options like herbal remedies or cosmetic procedures, clarifying evidence versus unproven claims. Importantly, pharmacists recognise the psychosocial burden of

Table I

Therapy	Mechanism of action	Notes	Efficacy and indications	Side Effects / Risks
Combined oral contraceptives (COCs)	Suppress luteinizing hormone (LH) → ↓ ovarian androgen production; ↑ hepatic SHBG → ↓ free testosterone[1,9]	Widely used as initial treatment	First-line therapy; reduce hirsutism scores;[9] newer progestins such as desogestrel, drospirenone, cyproterone acetate may offer better efficacy[6,15]	Headache, nausea, ↑ risk of venous thromboembolism with some progestins[9,15]
Antiandrogens – spironolactone	Blocks androgen receptors; ↓ adrenal androgens[6,9]	Requires contraception when used	Second-line / adjunct therapy: Effective for hirsutism; added if COCs suboptimal after 6 months[9]	Hyperkalaemia, menstrual irregularities, fatigue; contraindicated in pregnancy[9,15]
Antiandrogens – cyproterone acetate	Progestin with antiandrogenic action; inhibits 5α-reductase and androgen receptors[6]	Widely used in Europe/ South Africa (Mikiel 2020)[16]	**Second-line/alternative first-line (in COC combinations)**; marked reduction in hirsutism; often combined with oestrogen in COCs[6,9]	↑ Risk of thromboembolism[15]
Antiandrogens – finasteride	Inhibits 5α-reductase → ↓ conversion of testosterone to DHT[9]	Requires contraception; less effective than spironolactone	Second-line/adjunct therapy: provides additive effect with spironolactone for hirsutism[9]	Off-label in women[15]
Antiandrogens – flutamide	Non-steroidal androgen receptor blocker[6]	Not recommended by Endocrine Society[9]	**Not recommended** despite efficacy due to **high risk of severe hepatotoxicity,** including acute liver failure; safer alternatives preferred[9,16]	Severe hepatotoxicity, including risk of acute liver failure[9,16]
Topical eflornithine (vaniqa)	Inhibits ornithine decarboxyla→ ↓ hair growth[14]	Must be applied twice daily; recurrence after stopping; enhances laser efficacy[11,12]	Adjunct therapy: reduces facial hair thickness (↓26%) and length (↓23%) after 24 weeks;[12] effect seen after ~8 weeks[3]	Local irritation: acne, pseudofolliculitis barbae, itching, tingling[11,12]
Glucocorticoids	Suppress adrenal androgen production[9]	Reserved for adrenal causes[9]	**Indicated in NC-CAH (adrenal hyperandrogenism); not first-line for PCOS-related hirsutism** due to systemic side effects[9]	Long-term: weight gain, mood changes, osteoporosis[6]
Insulin sensitizers (metformin)	↓ Insulin → ↓ circulating androgens[17,18]	Mainly for PCOS metabolic features[18]	Adjunct therapy: may improve hirsutism in PCOS,[6] but not first-line[9]	GI upset, lactic acidosis (rare)[6]
GnRH Agonists	Suppress LH & FSH → ↓ ovarian androgen production[9]	Only for resistant/severe cases [9,15]	Third-line therapy: can reduce hirsutism in severe hyperandrogenism[15]	Hot flashes, bone loss, menopausal symptoms[9]

Table II

Herbal/Natural treatment	Proposed mechanism	Notes/Limitations	Evidence and efficacy
Cyperus rotundus oil	Oestrogenic compounds; possible hormonal modulation[13]	Promising as topical option; more trials needed	Efficacy comparable to Alexandrite laser in reducing axillary hair growth (dark & white)[19]
Fennel (foeniculum vulgare) extract	Oestrogenic compounds; inhibits 5α-reductase[11]	Effect may be patient-specific	Shown to reduce hair thickness and growth in idiopathic hirsutism; mixed results in PCOS patients[20]
Glycyrrhiza glabra (liquorice) gel	Oestrogenic and anti-androgenic activity[3]	Best studied as an adjunct	Combined with Alexandrite laser: significantly enhanced hair reduction in hirsutism[16]
Mentha spicata (spearmint) tea	Lowers free and total testosterone[1]	Safe, accessible dietary approach	Clinical studies: improved perceived hirsutism in women with PCOS[15]
Serenoa repens (saw palmetto) cream	Inhibits 5α-reductase[2]	Limited trial data	Topical application reduced facial hair counts[13]
Azadirachta indica (neem) and Zingiber officinale (ginger)	Anti-androgenic and follicle inhibitory effects[3]	Ginger may directly inhibit follicle growth	Trials: efficacy comparable to controls; reduced testosterone and mFGS in PCOS-related hirsutism[19]
Curcuma longa (turmeric) extract	Inhibits steroid 5α-reductase; anti-androgenic[4]	Potential dual systemic + topical benefits	Topical and oral: reduced underarm hair length, delayed regrowth; curcumin also improves PCOS symptoms[19]
Melaleuca alternifolia (tea tree oil) and lavender oil	Local anti-androgenic effect (mechanism unclear)[5]	Evidence limited; mechanism still under study	Spray combination ↓ hair diameter and Ferriman-Gallwey scores in mild idiopathic hirsutism[19]
Vitamin D (high-dose supplementation)	Hormonal regulation; ↓ androgens in PCOS[6]	More data needed on dosing and safety	Improved vitamin D levels and lowered androgen levels in women with raised BMI[15,20]
Microbiota modulation (probiotics, prebiotics, diet)	Affects hormonal regulation, inflammation, insulin resistance[7]	Still experimental; future adjuvant strategy	Emerging evidence: possible role in hirsutism pathogenesis[13]

hirsutism, including its impact on self-esteem and quality of life, and are well-positioned to offer empathetic support or referral to mental health services.[9] By collaborating with endocrinologists, dermatologists, and gynaecologists, pharmacists ensure continuity of care, contribute to safer, individualised treatment, and ultimately empower women to manage their condition more effectively.[10]

Future perspectives

Hirsutism care is moving toward mechanism-targeted, combination, and personalised strategies that balance efficacy with safety and quality of life. On the pharmacologic front, next-generation anti-androgen approaches are in view: selective androgen-receptor degraders/modulators (SARDs/SARMs) to blunt follicular AR signalling with fewer systemic effects; topical 5-α-reductase and steroidogenic enzyme inhibitors (CYP17A1, HSD3B, HSD17B) to localise action to skin/hair follicles; and optimised eflornithine delivery (higher-retention vehicles, microneedles) and fixed-dose combinations (e.g., eflornithine + topical anti-androgen) to accelerate onset and durability.[13] For PCOS-associated hirsutism, metabolic disease–modifying agents are reshaping the terrain: GLP-1 receptor agonists (± metformin) and inositol isomers may reduce androgen drive indirectly via weight loss and insulin sensitisation; future trials will clarify dose, duration, and comparative effectiveness versus current first-line regimens.[11]

Energy-based devices are evolving from hair removal toward adjunctive, protocolised regimens: newer diode/picosecond lasers, improved cooling, and sequential laser + pharmacologic protocols (e.g., laser + eflornithine/liquorice) aim to extend remission intervals and benefit lighter or hormonally active hair. Radiofrequency microneedling and photothermal combinations are under study for refractory cases and for patients who cannot tolerate systemic therapy.[14]

Biology-driven frontiers include the skin-gut microbiome-endocrine axis, where targeted pro-/prebiotics and dietary modulation could attenuate inflammation, insulin resistance, and local androgen signalling. Parallel work on follicular immuno-endocrine crosstalk (e.g., inflammatory cytokines, dermal papilla pathways) may yield non-hormonal topical inhibitors with favourable safety in reproductive-age patients.[1]

Care delivery is trending to personalised, longitudinal management. Pharmacogenomics (AR polymorphisms, drug-metabolising enzymes) and digital phenotyping (standardised photo-tracking, AI-assisted hair counts, patient-reported outcomes) can individualise treatment selection and objectively track response. Remote monitoring and clinical decision support will help titrate therapy over the 3–6-month response window, flag adverse effects (e.g., hyperkalaemia with spironolactone), and sustain adherence. Finally, future trials are prioritising patient-centred endpoints – time to visible benefit, remission durability, QoL, and cost-effectiveness – so that regimens can be tailored to fertility plans, comorbidities (obesity, insulin resistance), and cultural/cosmetic preferences.[2]

The next decade will likely deliver skin-targeted anti-androgens, smarter combinations with energy devices, metabolic disease–modifying adjuncts for PCOS, and data-driven personalisation — shifting hirsutism care from one-size-fits-all to precise, durable, and patient-defined outcomes.

Conclusion

Hirsutism is a common and impactful condition requiring a nuanced, often multidisciplinary, approach to management. Understanding the underlying aetiology, whether it be PCOS, idiopathic hirsutism, NC-CAH, or rarer causes, is crucial for effective treatment.[18] While cosmetic interventions provide immediate relief, long-term pharmacological therapies are often necessary to address the hormonal drivers of hair growth. Combination therapy, such as eflornithine cream with laser treatment, offers superior and faster results. Emerging herbal remedies and insights into the microbiota offer promising avenues for future complementary treatments.[17] Ultimately, successful management extends beyond physical hair removal to include supportive counselling and addressing the significant psychosocial and financial burdens experienced by affected women, thereby improving their overall quality of life. Continued research in diverse populations is needed to validate findings, explore long-term efficacy, and refine treatment guidelines.

Conflict of interest

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ORCID

RM Moosa-Battey https://orcid.org/0000-0002-1953-143X

KC Mbara https://orcid.org/0000-0002-8687-001X

References

1. Barbieri RL, Ehrmann DA, Crowley WF Jr. Pathophysiology and causes of hirsutism. In: UpToDate. Waltham (MA): UpToDate Inc.; 2022.
2. Matheson E, Bain J. Hirsutism in women. Am Fam Physician. 2019;100(3):168-75. https://doi.org/10.5771/97815381038821-168.
3. Kanbour SA, Dobs AS. Hyperandrogenism in women with polycystic ovarian syndrome: Pathophysiology and controversies. Androg Clin Res Ther. 2022;3(1):22-30. https://doi.org/10.1089/andro.2021.0020.
4. Pathania YS, Budania A, Rafi S, Kumar A. Psychosocial and financial impact of facial hair among female patients of hirsutism: A cross-sectional study. J Cosmet Dermatol. 2023;22(6):1906-1910. https://doi.org/10.1111/jocd.15655.
5. Spritzer PM, Marchesan LB, Santos BR, Fighera TM. Hirsutism, normal androgens and diagnosis of PCOS. Diagnostics (Basel). 2022;12(8):1922. https://doi.org/10.3390/diagnostics12081922.
6. Hohl A, Ronsoni MF, Oliveira M. Hirsutism: Diagnosis and treatment. Arq Bras Endocrinol Metabol. 2014;58(2):97-107. https://doi.org/10.1590/0004-2730000002923.
7. Yildiz BO, Bolour S, Woods K, Moore A, Azziz R. Visually scoring hirsutism. Hum Reprod Update. 2010;16(1):51-64. https://doi.org/10.1093/humupd/dmp024.
8. Amjad M, Jameel R, Liaqat T. Lived experiences of women with hirsutism: A phenomenological inquiry. J Postgrad Med Inst. 2023;37(3):213-20. https://doi.org/10.54079/jpmi.37.3.3184.
9. Martin KA, Chang RJ, Ehrmann DA, et al. Evaluation and treatment of hirsutism in premenopausal women: An Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2008;93(4):1105-20. https://doi.org/10.1210/jc.2007-2437.
10. Ozdemir S, Ozdemir M, Görkemli H, Kiyici A, Bodur S. Specific dermatologic features of

Full list of references available on request

Cognitive enhancers in South Africa: Regulation, ethics, and evidence in an international context

M Karolia,[1] N Schellack,[1] M Pretorius[2]

[1] Department of Pharmacology, School of Medicine, University of Pretoria, South Africa.

[2] Department of Human Resources, University of Pretoria, South Africa

Corresponding author, email: natalie.schellack@up.ac.za

Abstract

Background: Nootropics are a wide range of substances, including prescription medications and natural supplements that are indicated for the enhancement of cognitive function. Regulatory approaches differ locally and internationally with notable discrepancies in the regulation of synthetic nootropics compared to natural nootropics. These differences in regulations raise concerns regarding safety, evidence standards, and ethical use among healthy individuals.

Aim and objectives: To map the existing evidence on pharmacological classification, regulation, and ethical considerations of nootropics globally, with specific reference to nootropics available in South Africa.

Methods: This paper employs two methodologies to examine the regulation and use of cognitive enhancers in South Africa. A comprehensive scoping review, conducted in accordance with PRISMA and JBI guidelines, synthesised evidence from peerreviewed scientific publications and regulatory documents. A thematic analysis of South African regulatory texts was then undertaken to identify key regulatory themes related to cognitive enhancer scheduling and oversight. Building on these findings, two case studies were incorporated: first, a comparison of methylphenidate scheduling across countries identified in the scoping review; and second, an evaluation of the evidence supporting the use of two natural nootropics, phosphatidylserine and *Hericium erinaceus*, currently available in South Africa. Together, these approaches provide an integrated view of the scientific evidence base and regulatory landscape shaping access to, and governance of, cognitive enhancers in the South African context.

Results: The search returned 1686 records, from which 124 studies met the inclusion criteria. A scoping review of these studies identified variability in global regulatory classifications, evidence requirements, and ethical stances regarding nootropic use. Most research originated from high-income countries, with limited studies from South Africa. Thematic analysis highlighted three consistent themes: safety and efficacy, regulatory inconsistency, and ethical considerations. The methylphenidate case study showed varied scheduling between countries, reflecting differences in regulatory frameworks. Evidence for natural nootropics such as phosphatidylserine and *Hericium erinaceous* demonstrated limited evidence, resulting in minimal support for cognitive benefits and underscoring the need for more robust clinical research.

Conclusion: The results of the study show that nootropic regulation differs significantly across countries. Synthetic nootropics such as methylphenidate are well-regulated, but natural nootropics like *Hericium erinaceous* and phosphatidylserine often fall into regulatory gaps, as the evidence supporting their cognitive benefits remains limited. Across the studies, safety, efficacy, and ethical concerns, particularly regarding fairness and autonomy were recurring discussions. In South Africa, the lack of local data and unclear regulatory classification of natural nootropics underscores the need for increased local research efforts and clearer guidance to support safe and responsible use.

Keywords: ATC classification, cognitive enhancers, ethics, nootropics use, regulations

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Introduction

Nootropics, also known as cognitive enhancers, are a diverse group of substances, designed to enhance cognitive functions such as memory, focus, and creativity.[1] The term was coined in 1972 by Prof. Dr Corneliu Giurgea, following his work on the synthetic prototype piracetam, which demonstrated cognitive benefits without significant side effects.[2,3] Since then, interest in nootropics has expanded across students, professionals (including scientists and clinicians), and military populations, contributing to a rapidly growing global nootropics market estimated to surpass USD 4 billion by 2025.[3,4] Despite this increased use, the efficacy, safety, and ethical implications of nootropic use, particularly among healthy individuals remain contested.[5]

Nootropics can be broadly categorised into synthetic substances, such as methylphenidate and modafinil, and natural products, like *Hericium erinacous* (lion's mane mushroom) and phosphatidylserine.[1] However, the legal and regulatory frameworks governing these substances differ substantially across countries.[6] For example, modafinil is a Schedule IV controlled substance in the United States under the Controlled Substances Act, requiring a prescription, whereas in the United Kingdom it is classified as Schedule IV under the Misuse of Drugs Regulations of 2001, which states that possession without prescription is not an offence but supply without one remains illegal.[6,7] These differences illustrate how national policies influence access and potential misuse.

In South Africa, the regulatory landscape is shaped by the Medicines and Related Substances Act 101 of 1965 (MRSA). The South African Health Products Regulatory Authority (SAHPRA)[8] operates under the Act's provision as the national regulator for

all health products, ensuring they are safe, effective, and of good quality before reaching the public. Through this mandate, it protects public health, prevents misuse of prescription medicines, and oversees the lawful sale and use of medical products.

Synthetic nootropics such as methylphenidate are scheduled medicines that require a prescription in South Africa, while natural nootropics such as *Hericium erinaceous* and phosphatidylserine are sold as over-the-counter supplements that are less stringently regulated.[8] This regulatory gap was highlighted by a 2022 South African Supreme Court of Appeal ruling, which noted that many natural or plant-based products do not fall under the MRSA's definition for a medicine that is broadly defined as any substance used or claimed to diagnose, treat, prevent disease, or alter bodily or mental functions.[9] As a result, the Court called for a more suitable regulatory approach for natural health products, including those used in traditional medical systems.

In the context of nootropics, the absence of standardised regulations for unscheduled and natural nootropics poses significant challenges in ensuring responsible use and guiding the development of safe and effective cognitive-enhancing therapies.[10] Standardised international classification systems also lack consistency. The World Health Organization's (WHO) Anatomical Therapeutic Chemical (ATC) Classification System provides classification for recognised drugs based on their therapeutic, pharmacological, and chemical properties.[11] Methylphenidate and modafinil for example, fall under N06BA (psychostimulants), while many natural nootropics have no ATC classification at all, leaving them in regulatory grey zones.[12]

Ethical concerns associated with nootropic use include issues of autonomy, fairness, and potential coercion, particularly in academic and professional settings where individuals may feel pressured to use them to maintain competitiveness, thereby blurring the line between voluntary and socially driven use.[13-15] Additionally, cost disparities may create inequitable access, raising concerns about distributive justice.[16] These considerations underscore the need for regulatory frameworks that promote safety while respecting individual choice and ensuring equitable access.

This scoping review therefore aims to conduct a situational analysis of the use and regulation of scheduled and unscheduled nootropics in South Africa and internationally and is organised around four core research questions:

1. *Pharmacological classification:* How are nootropics classified within the South African and global pharmaceutical markets?
2. *Regulatory framework:* What regulatory frameworks govern nootropics in South Africa and globally?
3. *Benefits and challenges:* What are the potential benefits, challenges, and ethical considerations associated with nootropics use in South Africa and globally?
4. *Case study analysis:* What is the regulatory status and evidence base for the indication of two natural nootropics available in South Africa?

By addressing these research questions, this review clarifies the evolving landscape of nootropic regulation, highlights the ethical considerations surrounding cognitive enhancement, and evaluates the scientific evidence guiding the responsible use of nootropics.

Methodology

Study aim, design, and setting

Aim

This study aimed to comprehensively examine the pharmacological classification, regulation, safety, efficacy, and ethical considerations of natural and synthetic nootropics in the global context, with a specific focus on South Africa.

Design

A multi-method design was used, consisting of a scoping review conducted according to the Joanna Briggs Institute (JBI) methodology and reported in line with PRISMA-ScR guidelines.[17,18] Two case studies were conducted. The first examined the international scheduling of the synthetic nootropic methylphenidate, and the second examined the scientific evidence supporting the safe use of two natural nootropics found in South Africa, *Hericium erinaceous* (lion's mane mushroom) and phosphatidylserine. A qualitative thematic analysis of South African regulatory documents was also conducted.

Setting

The study examined the global landscape of nootropic use and regulation, with an emphasis on South African policies, regulatory frameworks, and market availability.

Description of scoping review processes, interventions and comparisons

Eligibility

Eligibility criteria were informed by the Population–Concept–Context (PCC) framework. The population included individuals using or considering nootropics for cognitive enhancement. The concept focused on pharmacological classification, regulation, scheduling systems, safety, efficacy, and ethical concerns related to nootropic use. The context encompassed both global and South African regulatory and ethical environments.

Included studies comprised original research, reviews, guidelines, editorials, commentaries, case reports, and policy documents addressing classification, regulation, safety, efficacy, or ethical aspects of nootropics. Relevant grey literature on South African regulation was also considered. There were no restrictions on publication period or clinical setting. Articles unrelated to nootropics or their regulation, as well as non-English publications, were excluded. The final search was completed on 12 July 2024.

Search strategy

A comprehensive, multi-session search was conducted across PubMed, Scopus, and Web of Science between 1–12 July 2024.

Searches used combinations of controlled vocabulary and keywords, including:

- nootropics, cognitive enhancers, smart drugs
- regulation, classification, ethics, policy.

Boolean operators (e.g., (nootropics OR "cognitive enhancers") AND (regulation OR ethics OR safety)) were applied consistently. Reference lists of included studies were screened to identify additional sources.

Manuscript selection and data extraction

All search results were imported into EndNote for reference management and transferred to Rayyan AI for screening. Duplicate records were removed. Two reviewers (MK, NS) independently screened titles and abstracts, and disagreements were resolved by a third reviewer (MP). Full-text screening followed the same process.

Data charting followed JBI guidelines and included: authorship, year of publication, study type and level of evidence, nootropic class investigated, regulatory or ethical focus, country of origin, and key findings related to safety, efficacy, and regulation.

Data charting, collation, summarization, and synthesis

Data was charted into structured tables. Findings were synthesised descriptively, focusing on: global trends in nootropic classification and regulation; safety and efficacy evidence; ethical considerations; country-specific regulatory frameworks and scheduling patterns. Narrative synthesis was used to contextualise similarities, differences, and gaps across jurisdictions.

Quality assurance and statistical analysis

Cohen's Kappa was calculated to assess inter-reviewer agreement during both title/abstract and full-text screening. Descriptive statistics were used to summarise study characteristics (e.g., publication types, geographic distribution).

Qualitative thematic analysis of South African regulatory documents

A qualitative thematic analysis was conducted to identify regulatory principles governing nootropics in South Africa.

The document set included key legislations, and SAHPRA guidelines.[8,19-22]

Table I: Inclusion criteria for selecting articles to be included in the scoping review

Inclusion Criteria	1. Articles written in the English language only 2. All peer-reviewed publication types and selected grey literature 3. Studies conducted in healthy humans 4. Studies related to the use or regulation of nootropics

Analytical process

Documents were imported into ATLAS.ti., open coding was conducted to identify regulatory concepts, supported by AI-assisted coding suggestions. Codes were grouped using axial coding to develop broader categories. Final themes were generated through comparison across documents. Themes were integrated with scoping review findings to contextualise the South African regulatory landscape.

This process enabled identification of key regulatory problems, including scheduling inconsistencies, gaps in oversight of natural products, and evolving frameworks for complementary medicines.

Case study methodology

Case Study 1: Methylphenidate scheduling across countries

Countries identified in the scoping review formed the basis of comparative analysis. National legislation, scheduling schedules, and regulatory databases were reviewed. A numerical coding system was used to compare scheduling classes, prescription requirements, and restrictions on off-label use.

Case Study 2: Natural nootropics in the South African market

Two commonly used natural nootropics, *Hericium erinaceous* and phosphatidylserine, were selected. A targeted literature review examined: mechanisms of action, recommended dosages, safety and adverse effect profiles, clinical efficacy evidence, regulatory status in South Africa and comparable jurisdictions.

Findings were synthesised to evaluate their suitability within current regulatory frameworks.

Ethical considerations

Although no human participants were involved in this study, ethical approval was obtained through the University of Pretoria's Faculty of Health Sciences Research Ethics Committee (REC). (Reference 176/2024). Approval was granted on 11 April 2024 and remained valid for a period of one year only until 11 April 2025.

Limitations

This review has several limitations.

Language bias: Only English-language publications were included.

Publication bias: Reliance on peer-reviewed literature may exclude relevant unpublished data or grey literature sources.

Limited high-quality evidence: Few randomised controlled trials or systematic reviews specifically addressed nootropic use and regulation.

Rapidly evolving field: Given the fast-paced nature of nootropic research, policies and classifications may change after the search period. No data restrictions were applied, allowing inclusion of both historical and current data.

Results

Summary of the literature search

Case Study 1: Methylphenidate

- Methylphenidate was the most frequently referenced prescription nootropic in South African literature.
- It was selected for comparative analysis of regulatory classifications across different countries.
- The analysis examined:
  - Scheduling category of methylphenidate in each country.
  - Availability with or without a prescription.
  - Legality of off-label use in each jurisdiction.
- Regulatory classifications vary globally, for example:
  - Schedule 1 in the Netherlands.
  - Schedule 8 in Australia.
  - Schedule 6 in South Africa.
- In all countries studied, methylphenidate:
  - Requires a prescription for legal access.
  - Is not legally available for off-label use.

A total of 1686 references were retrieved across all the selected databases (Figure 1). After removal of 609 duplicates, 1077 articles remained for title and abstract screening. Of these, 823 articles were excluded, resulting in 254 articles progressing to full-text retrieval. Full texts could be obtained for 173 articles, of which 124 articles met the inclusion criteria for the final scoping review. Inter-reviewer agreement calculated using Cohen's Kappa statistic demonstrated moderate agreement for title and abstract screening ($\kappa = 0.415$, $p < 0.001$) and slight agreement for full text screening ($\kappa = 0.150$, $p < 0.001$).

Characteristics of the study

Details of the included studies are listed in Table II a and b. The list of 124 papers and full publishing details can be found in the Supplementary material appendices. The 124 included studies demonstrated substantial methodological and thematic heterogeneity. Narrative reviews (25%; *n* =31) and commentaries/editorials (12%; *n* = 15) were the most common study designs, while 46% (*n* = 58) of articles were categorised as "other" or non-specified. The majority of studies were classified as level V (43%; *n* = 53) or VII (28%; *n* = 35) evidence.

Geographically, 61% (*n* = 76) of studies originated from high-income countries, with the United States (27%; *n* = 33) and United Kingdom (15%; *n* = 18) most represented. The remaining studies were conducted in middle- and low-income countries. Only three studies (2%) included data directly relevant to South Africa, highlighting a substantial evidence gap.

Regarding populations, studies most frequently focused on healthy adults (36%; *n* = 44) and students (20%; *n* = 25), although several examined multiple groups.

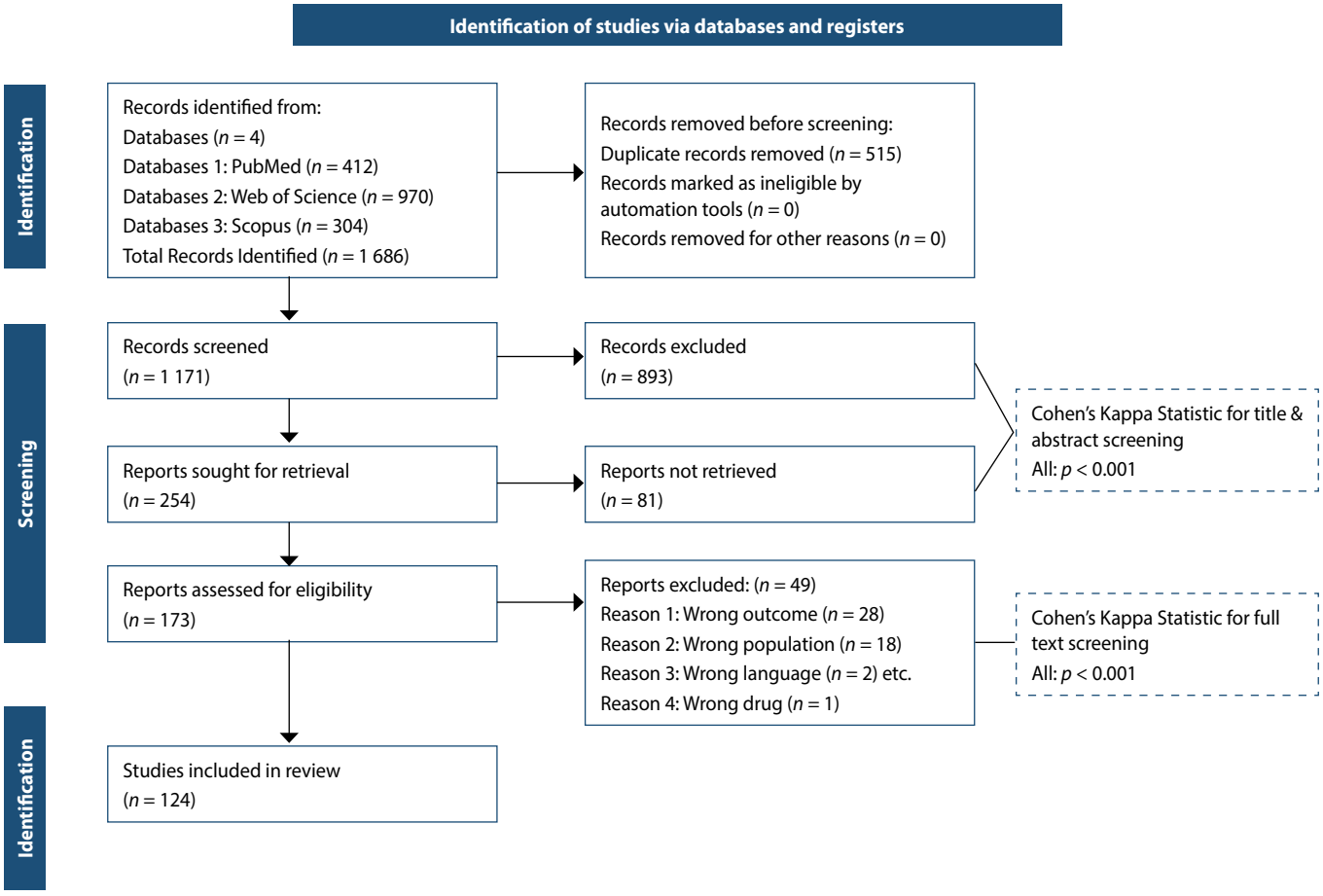


Figure 1: PRISMA-ScR flow diagram[18]

Table II (a): Characteristics of studies on cognitive enhancers (*n* = 124)

COUNTRIES	% of peer-reviewed publications	Number of publications (*n*)
High income countries		
United Kingdom	19%	33
United States of America	18%	32
Italy	8%	14
Upper-middle-income countries		
South Africa	1.1%	2
India	5.1%	9
Study design		
Level I	6%	7
Level II	5%	6
Level III	2%	3
Level IV	13%	16
Level V	42%	52
Level VI	11%	13
Level VII	22%	27
Population		
Healthy individuals	35%	43
Students	20%	25
Professionals	8%	10
Clinicians	8%	10
Military	7%	9
Employees	6%	7
Academics	5%	6
Athletes	2%	2
Other	9%	11
ATC nootropics		
Methylphenidate	17%	21
Modafinil	16%	20
Amphetamine	12%	15
Caffeine	8%	10
Piracetam	5%	6
Functional classification of non-ATC nootropics		
Dietary supplements	24%	30
Herbal nootropics	28%	34
Amino acids	6%	7
Stimulants	8%	10
Other	39%	47

Methylphenidate (37%; *n* = 45) and modafinil (28%; *n* = 34) were the most frequently discussed substances under ATC code N06BA. Among non-ATC classified substances, dietary supplements (12 mentions) and herbal nootropics (10 mentions) were most common.

Thematically, ethical considerations were most prevalent (42%; *n* = 44), followed by safety and efficacy concerns (30%; *n* = 37), and regulatory challenges (25%; *n* = 31). Studies addressed an average, of 1.85 themes, highlighting the multifaceted nature of cognitive enhancement.

These findings illustrate the international regulatory strictness surrounding prescription

The scheduling classification, prescription requirements, and legality of off-label methylphenidate use across various countries are illustrated in Figure 2.

Case study 2: Hericium erinaceous(lion's mane mushroom) and phosphatidylserine

- Lion's mane mushroom was mentioned in 6 studies, but only 1 study explored it in depth.
  - The key study by Saitsu et al.:[23]
    - Randomised, double-blind, placebo-controlled trial.
    - Evaluated cognitive improvements over 12 weeks in healthy individuals.
    - Found significant improvements in cognitive function and neuroprotection.
  - Other articles described its neuroprotective and memory-enhancing properties.[24-26]
  - However:
    - Clinical trials are limited.[27]
    - Current evidence is insufficient to confirm safety and efficacy in healthy populations.[27]
  - Phosphatidylserine (PS)
  - PS was mentioned in 4 studies, and discussed in detail in 3 studies.
  - One study noted that the overall evidence for cognitive efficacy and neuroprotection is weak.[24-26,28-30]
  - Glade et al. reported that:[31]
    - Doses of 300–800 mg/day are considered safe and potentially effective for cognitive support.

Thematic analysis

The thematic analysis of the scoping review and AI-coded themes revealed significant convergence across several key areas in cognitive enhancer research. Ethical considerations emerged as the most prevalent theme in the scoping review (42% of studies), aligning closely with the high frequency of "Ethics" (16 occurrences) in the AI analysis. This convergence underscores the centrality of ethical debates in the field of cognitive enhancement. Safety and efficacy concerns ranked second in the scoping review (30%), reflecting the importance of these issues in the literature. While not explicitly coded as such in the AI analysis, these concerns likely contribute to the high frequency of "Health Care" (45 occurrences) and "Compliance" (17 occurrences) themes. Regulatory challenges, identified in 25.% of scoping review studies, showed strong alignment with the AI-coded themes of "Legal" (159 occurrences) and "Regulation" (49 occurrences). This convergence highlights the significant focus on legal and regulatory aspects of cognitive enhancers across both analyses. To quantify the thematic convergence, we calculated a simple convergence ratio. Convergence ratio = Number of aligned themes / Total number of unique themes = 4 / (15 + 16 - 4) = 4 / 27 ≈ 0.148 or 15%. This moderate level of convergence suggests reliability in the identified themes while also indicating areas of divergence that merit further investigation. Clustering related themes revealed broader categories:

1. Ethical and social issues: Encompassing ethical considerations, societal concerns, fairness and equity, social justice, and human rights.

KEY:
- Scheduling level: Scale 0–8 (higher = stricter regulation)
- Prescription required: 0 = Yes, 1 = No
- Off-label use: 1 = Legal, 2 = Illegal

Figure 2: Radar chart illustrating the scheduling classification, prescription requirements, and legality of off-label methylphenidate use across various countries

2. Regulatory and legal issues: Including regulatory challenges, legal and access issues, compliance, and health regulations.
3. Health and safety: Covering safety and efficacy concerns, health concerns, and long-term effects.
4. Practical applications: Developing policies to guide the use of cognitive enhancers in academic/professional settings.

Unique themes emerged from each analysis, pointing to areas for further research. The scoping review highlighted themes such as substance abuse potential and neurobiology of cognition, while the AI analysis identified themes like professional conduct and human rights. These differences suggest potential gaps in the current literature and opportunities for more comprehensive research approaches. In conclusion, the convergence of themes across both analyses reinforces the multifaceted nature of cognitive enhancer research, emphasising the need for interdisciplinary approaches that address ethical, legal, health, and societal implications simultaneously. Figure 3 presents a network view of the themes identified through and visualised using Atlas.ti.

Table II (b): Characteristics of studies on cognitive enhancers (*n* = 124)

Characteristic	Category	Number (%)	Additional information
Study designs			
	Review (narrative)	31 (25.0%)	
	Commentary/Editorial	15 (12.1%)	
	Debate/Discussion	7 (5.6%)	
	Cross-sectional studies	6 (4.8%)	
	Systematic reviews	4 (3.2%)	
	RCTs	3 (2.4%)	
	Other/Not specified	58 (46.8%)	
Level of evidence			
	I	6 (4.8%)	
	II	5 (4.0%)	
	III	2 (1.6%)	
	IV	10 (8.1%)	
	V	53 (42.7%)	
	VI	13 (10.5%)	
	VII	35 (28.2%)	
Geographical distribution			Total studies: 124
High-income countries		76 (61.3%)	
	United States	33 (26.6%)	Mode of geographical focus
	United Kingdom	18 (14.5%)	
	Canada	7 (5.6%)	
	Germany	5 (4.0%)	
	Switzerland	5 (4.0%)	
	Australia	3 (2.4%)	
	Other high-income	5 (4.0%)	
Upper-middle-income countries		7 (5.6%)	
	South Africa	5 (4.0%)	
	Poland	1 (0.8%)	
	Turkey	1 (0.8%)	
Lower-middle-income countries		2 (1.6%)	
	India	2 (1.6%)	
Low-income countries		0 (0%)	
Not specified or multiple		39 (31.5%)	
Population focus*			
	Healthy individuals	43 (35.5%)	
	Students	25 (20%)	
	Professionals	10 (9.7%)	
	Cognitive disorder patients	7 (5.6%)	
	Athletes	2 (1.6%)	
	Elderly	2 (1.6%)	
	Healthcare workers	1 (0.8%)	
	Clinicians	10 (8%)	
	Academics	6 (5%)	
	Not specified	28 (22.6%)	
Key Themes*			Total themes: 230
	Ethical considerations	52 (41.9%)	
	Safety and efficacy concerns	37 (29.8%)	
	Regulatory challenges	31 (25.0%)	
	Societal concerns	22 (17.7%)	
	Cognitive enhancement in academic/professional settings	20 (16.1%)	
	Legal and access issues	15 (12.1%)	
	Benefits vs. risks analysis	10 (8.1%)	
	Fairness and equity in access and use	9 (7.3%)	
	Health concerns	8 (6.5%)	
	Increased use of nootropics	7 (5.6%)	
	Substance abuse potential	5 (4.0%)	
	Coercion and autonomy	4 (3.2%)	
	Public policy implications	4 (3.2%)	
	Long-term effects	3 (2.4%)	
	Neurobiology of cognition	3 (2.4%)	
ATC classification of nootropics			Total mentions: 101
N06BA (Centrally acting sympathomimetics)		72 (71.3%)	
	Methylphenidate (N06BA04)	37 (36.6%)	
	Modafinil (N06BA07)	28 (27.7%)	
	Amphetamine (N06BA01)	7 (6.9%)	
N06BC (Xanthine derivatives)		14 (13.9%)	
	Caffeine (N06BC01)	14 (13.9%)	
N06DA (Anticholinesterases)		9 (8.9%)	
	Donepezil (N06DA02)	9 (8.9%)	
N06BX (Other psychostimulants and nootropics)		6 (5.9%)	
	Piracetam (N06BX03)	4 (4.0%)	
	Others	2 (2.0%)	
Functional classification of non-ATC nootropics			Total mentions: 42
Dietary Supplements	12		
Herbal Nootropics	10		
Amino Acids	5		
Stimulants	8		
Other	7		

*Note: Some studies focused on multiple populations or themes, so percentages may sum to more than 100%.

Statistical analysis

Total number of studies: 124
Total number of populations: 127 (mean: 1.02 populations per study)
Total number of key themes: 230 (mean: 1.85 themes per study)
Total number of nootropics mentioned: 114 (72 ATC classified, 42 non-ATC classified)
Mean number of nootropics per study: 0.92

Discussion

Global patterns of nootropic use and evidence gaps

This scoping review reveals the complex landscape of nootropic use and regulation, and the rapidly expanding volume of literature on nootropics, with research output surging from 2013 onwards. This growth reflects increasing public interest in cognitive enhancement, particularly among healthy individuals, students, professionals such as scientists and clinicians, military personnel, and users of traditional medicines.[32-34] Maier et al. reported that 20% of respondents across 60 countries had used cognitive enhancers off-label, highlighting the international relevance of this topic.[35]

Despite the breadth of publications, the strength of evidence remains limited. Most included studies were narrative reviews or commentaries of lower evidence levels, and high-quality clinical trials were limited. As a result, the safety and efficacy of many widely used nootropics particularly in healthy populations remains uncertain.[36] Although some studies suggest that nootropics demonstrate cognitive benefits in clinical or impaired populations, translating these findings to healthy users is complex and insufficiently supported by robust research.[37]

The literature on nootropics also reveals a geographical skew, with a disproportionate focus on higher-income countries, particularly the United States and the United Kingdom. This bias underscores the need to expand more research efforts into low- and middle-income countries, to develop a comprehensive understanding of nootropic use and regulation across varying socioeconomic and cultural settings.

Global regulatory challenges and divergence

The regulatory landscape for nootropics varies significantly across countries. This was demonstrated by the methylphenidate case study which showed the variation of the drug's classification between Schedule 1 to Schedule 8, depending on the jurisdiction.

A further regulatory challenge is the inconsistent application of established classification systems, such as the WHO ATC system.[11] While synthetic agents are classified within the framework, many natural nootropics are not. This absence of uniform classification presents challenges for regulatory bodies in assessing and managing these substances effectively.

South African context: Regulation, evidence, and gaps

Although the study aimed to examine nootropic use within South Africa, only three studies originated from the country. This limited evidence reflects the urgent need for more comprehensive studies to be conducted in South Africa.

The document analysis of key South African regulatory texts provided valuable insights.[8,19-22] South Africa's primary medicines legislation (MRSA Act 101 of 1965) is designed specifically for regulating synthetic pharmaceuticals.[8] This creates a regulatory gap for complementary medicines, natural health products and traditional medicines. The 2022 South African Supreme Court of Appeal ruling confirmed that alternative health products require a separate regulatory pathway, thus reinforcing the concerns about ambiguity in oversight of natural nootropics.[9] Linking these regulations to the Constitution is crucial for creating regulatory frameworks that are effective, protect consumer safety, and ensure fair access to these substances.

Case study implications for South Africa

The two natural nootropics examined, *Hericium erinaceous* and phosphatidylserine, illustrate this lax in the South African regulatory framework. Both substances are marketed locally as cognitive enhancers, yet neither is regulated under the same stringent standards applied to Schedule 6 medicines like methylphenidate. Preclinical and small-scale clinical studies suggested potential cognitive benefits for both of these natural nootropics, but the evidence is limited, inconsistent, and based on small sample sizes.[38-40] Because these products fall into a grey area between complementary medicines and unregistered supplements, their regulatory status in South Africa remains unclear, raising concerns about product quality, safety, and efficacy.[36]

Ethical, social, and equity considerations

Across the literature and regulatory documents analysed, ethical considerations emerged as a dominant theme, with the key concerns including autonomy, fairness, and coercion.[14,41] This is due to increasing accessibility of cognitive enhancers which may result in individuals feeling pressured to use nootropics in competitive environments, exacerbating societal pressures to use these substances.[42] With regards to fairness, unequal access to cognitive enhancers could disadvantage lower-income groups.[43] These issues are particularly relevant in South Africa, where socioeconomic inequalities may amplify already existing disparities if access to cognitive enhancement results in the creation of unequal opportunities. This highlights the importance of addressing distributive justice in the broader conversation about nootropics use.

Conclusion

The findings of this review highlights the complex and evolving landscape of nootropic use and regulation, revealing significant gaps in evidence, inconsistent regulatory frameworks, and ethical concerns. Regulation of synthetic nootropics is well-defined under established pharmaceutical legislation, whereas natural nootropics including *Hericium erinaceous* and phosphatidylserine often fall into regulatory grey areas, creating uncertainties around safety, efficacy, and consumer protection.[44]

Ethical concerns related to fairness, autonomy, and socioeconomic inequality, emerged as dominant themes, particularly in academic, professional, and other competitive environments. The growing availability of cognitive enhancers may exacerbate pressures to use them, emphasising the importance of effective regulations and evidence-based guidelines.

As interest in cognitive enhancers continues to rise, coordinated scientific research, the development of ethical frameworks, and clear regulatory policies will be essential to protect public health while promoting equitable access and responsible use. The limited number of studies from South Africa (n = 3) further underscores the need for locally relevant research to inform policy and practice.

Recommendations for future research

Based on the findings and limitations of this scoping review, several recommendations for future research can be made. Robust efficacy and safety evidence: High-quality randomised controlled trials are needed to establish the benefits, risks and potential interactions of both synthetic and natural nootropics, especially in healthy populations and over long-term use.[37] Global representation: More research from low- and middle-income countries is required to counter geographic bias and provide a more comprehensive understanding of global nootropic use and regulation. Regulatory development and evaluation: Studies should explore regulatory frameworks capable of distinguishing between prescription-based nootropics and natural or dietary products, and assess how these frameworks can balance safety with accessibility.[41] Quality and standardisation of natural nootropics: Research should focus on standardised formulations, quality control, and product consistency to support safe, evidence-based use. Interdisciplinary approaches: More holistic and informed policies or practices should be developed by combining neuroscience, pharmacology, ethics, law and public health.[4]

Conflict of interest

The authors declare no conflict of interest.

Funding source

No funding was required.

Ethical approval

Prior to the commencement of the study, ethical approval was obtained from the University of Pretoria's Faculty of Health Sciences Research Ethics Committee. The ethics number is 176/2024 This article does not contain any studies with human or animal subjects.

ORCID

M Karolia https://orcid.org/0009-0006-1522-4826

N Schellack https://orcid.org/0000-0001-9690-6285

M Pretorius https://orcid.org/0009-0007-3563-6198

References

1. Malik M, Tlustos P. Nootropics as cognitive enhancers: Types, dosage and side effects of smart drugs. Nutrients. 2022;14(16):3367. https://doi.org/10.3390/nu14163367.
2. Partridge B, Bell S, Lucke J, Hall W. Australian university students' attitudes towards the use of prescription stimulants as cognitive enhancers: Perceived patterns of use, efficacy and safety. Drug Alcohol Rev. 2013;32(3):295-302. https://doi.org/10.1111/dar.12005.
3. Giurgea C, Salama M. Nootropic drugs. Prog Neuropsychopharmacol. 1977;1(3):235-473 https://doi.org/10.1016/0364-7722(77)90046-7.
4. Greely H, Sahakian B, Harris J, et al. Towards responsible use of cognitive-enhancing drugs by the healthy. Nature. 2008;456(7223):702-5. https://doi.org/10.1038/456702a.
5. Schifano F, Catalani V, Sharif S, et al. Benefits and harms of 'smart drugs' (nootropics) in healthy individuals. Drugs. 2022;82(6):633-47. https://doi.org/10.1007/s40265-022-01701-7.
6. Ragan CI, Bard I, Singh I. What should we do about student use of cognitive enhancers? An analysis of current evidence. Neuropharmacology. 2013;64:588-95. https://doi.org/10.1016/j.neuropharm.2012.06.016.
7. Drug Enforcement Administration. Scheduling actions controlled substances regulated chemicals. Justice USDo. United States: Drug Enforcement Administration; 2025. p. 21.
8. South African Medicines and Related Substances Act 101 of 1965. South Africa Government Gazette 1965. p. 32.
9. Minister of Health and Another v Alliance of Natural Health Products. Southern Africa Legal Information Institute; HIPR 195 (SCA); 11 April 2022.
10. Barit A. Legal and ethical considerations of pharmaceutical cognitive enhancer use in South Africa: Towards a legal framework. University of Pretoria; 2019. Available from: http://hdl.handle.net/2263/76764
11. World Health Organization [Internet]. Anatomical Therapeutic Chemical (ATC) Classification. Available from: https://www.who.int/tools/atc-ddd-toolkit/atc-classification.
12. DrugBank Online [Internet]. ATC Classification. Available from: https://go.drugbank.com/atc/N06B#.
13. Garasic MD, Lavazza A. Moral and social reasons to acknowledge the use of cognitive enhancers in competitive-selective contexts. BMC Med Ethics. 2016;17:18. https://doi.org/10.1186/s12910-016-0102-8.
14. Shaw D. Neuroenhancing public health. J Med Ethics. 2014;40(6):389-91. https://doi.org/10.1136/medethics-2012-101300.
15. Maslen H, Faulmuller N, Savulescu J. Pharmacological cognitive enhancement: How neuroscientific research could advance ethical debate. Front Syst Neurosci. 2014;8:107. https://doi.org/10.3389/fnsys.2014.00107.
16. Makridis C. Converging technologies: A critical analysis of cognitive enhancement for public policy application. Sci Eng Ethics. 2013;19(3):1017-38. https://doi.org/10.1007/s11948-012-9396-1.
17. Aromataris E, Lockwood C, Porritt K, Pilla B, Jordan Z [Internet]. JBI Manual for evidence synthesis. JBI. 2024. https://doi.org/10.46658/JBIMES-24-01.
18. Haddaway NR, Page MJ, Pritchard CC, McGuinness LA. PRISMA2020: An R package and Shiny app for producing PRISMA 2020-compliant flow diagrams, with interactivity for optimised digital transparency and open synthesis. Campbell Syst Rev. 2022;18(2):e1230. https://doi.org/10.1002/cl2.1230.
19. National Health Act No. 61 of 2003. South Africa Government Gazette 2004. p. 48
20. Health Professions Act 56 of 1974. South Africa Government Gazette 1974. p. 63
21. General Regulations Made In Terms Of The Medicine And Related Substances Act. South Africa Government Gazette 1965. p. 91
22. Drugs and Drug Trafficking Act. South Africa Government Gazette 1992. p. 361.
23. Saitsu Y, Nishide A, Kikushima K, Shimizu K, Ohnuki K. Improvement of cognitive functions by oral intake of Hericium erinaceus. Biomed Res. 2019;40(4):125-31. https://doi.org/10.2220/biomedres.40.125.
24. Tabassum N, Rasool S, Malik Z, Ahmad F. Natural cognitive enhancers. J Pharm Res. 2012;5:153-60.
25. Onaolapo AY, Obelawo AY, Onaolapo OJ. Brain ageing, cognition and diet: A review of the emerging roles of food-based nootropics in mitigating age-related memory decline. Curr Aging Sci. 2019;12(1):2-14. https://doi.org/10.2174/1874609812666190311160754.
26. Crespo-Bujosa HB, Suárez Rodríguez RLF. Nootropics: Phytochemicals with neuroprotective and neurocognitive enhancing properties. Eur J Clin Exp Med. 2019;17(3):250-5. https://doi.org/10.15584/ejcem.2019.3.9.
27. Abbott-Imboden C, Gonzalez Y, Utley A. Efficacy of the nootropic supplement Mind Lab Pro on memory in adults: Double blind, placebo-controlled study. Hum Psychopharmacol. 2023;38(4):e2872. https://doi.org/10.1002/hup.2872.
28. Singh P, Gupta A, Verma A. Herbal memory enhancer: A review. Pharma Research. 2013;10:96-109.
29. McDaniel MA, Maier SF, Einstein GO. "Brain-specific" nutrients: A memory cure? Nutrition. 2003;19(11):957-75. https://doi.org/10.1016/S0899-9007(03)00024-8.
30. Hofmeister EH, Muilenburg JL, Kogan L, Elrod SM. Over-the-counter stimulant, depressant, and nootropic use by veterinary students. J Vet Med Educ. 2010;37(4):403-16. https://doi.org/10.3138/jvme.37.4.403.
31. Glade MJ, Smith K. Phosphatidylserine and the human brain. Nutrition. 2015;31(6):781-6. https://doi.org/10.1016/j.nut.2014.10.014.
32. Larriviere D, Williams MA, Rizzo M, Bonnie RJ; AAN Ethics, Law and Humanities C. Respond-

Full list of references available on request

Appendix A: Supplementary material – Data Extraction Sheet available online: https://ojs.sabinet.co.za/index.php/sapj/article/view/3354

"Learn from yesterday, live for today" — Albert Einstein

Dr Seshnee Moodley

President, SAAHIP

The 2025/2026 SAAHIP term had been both demanding and rewarding. It required us to return to first principles, reaffirm our purpose, and realign our activities to the evolving needs of the profession. This process reinforced a clear message: the future of hospital pharmacy is relevant and promising but also depended on the strong foundations laid out by previous leaders. Our work has continuously been guided by SAAHIP's four foundational pillars i.e., collaboration, shared vision, commitment, and innovation. Well on our way into the 2nd quarter of 2026 and the new term 2026/2027, my hope is that there is renewed vigour and focus for the plans that we previously set out as SAAHIP.

I have been fortunate enough to be elected to my 2nd term of office as the President, during our National AGM which took place on 14 March 2026 and looking forward into 2026, SAAHIP has been invited to collaborate on two exciting National Pharmaceutical conferences i.e. South African Pharmaceutical Exhibition (SAPHEX) and South African Pharmacy Council (SAPC). These important collaborations will allow us to showcase hospital pharmacy and what the future of hospital pharmacy holds.

SAPHEX took place recently and the overall theme was 'Uniting Health Care Professionals'. The SAAHIP session was incredibly successful and provided a platform for our hospital pharmacists to showcase their success stories, followed by a robust panel discussion. I thank our 3 session speakers and session chair, Mr Kesentseng Jackson Mahlaba, for ensuring the chosen session theme was achieved i.e. 'Celebrating Success Stories in Hospital Pharmacy: Demonstrating Value, Innovation, and Impact.'

Across South Africa, hospital pharmacists have led innovations in clinical governance, antimicrobial stewardship, patient safety and service transformation. The SAAHIP session aimed to honour and showcase these successes from hospital pharmacists who have driven measurable improvements in patient outcomes, introduced novel service models, and demonstrated leadership in interdisciplinary healthcare. The topics presented in the session were:

1. Building Stewardship Culture: Successes from Antimicrobial Stewardship Teams in Public Sector Hospital. *Lebogang Molepo, Pharmacist at Pietersburg Hospital*
2. Collaborative Clinical Pharmacy Models in Hospital Care. *Kim Nagoor, Pharmacist at Netcare Digital Clinical Pharmacy Unit*
3. Leading Change from Within: Pharmacists as Innovators in Resource-Constrained Hospital Settings. *Bandela Mgoqi, Pharmacy Manager at Kalafong Tertiary Hospital*

We were also afforded the opportunity to join the 80th birthday celebrations of our Pharmaceutical Society of South Africa (PSSA) at SAPHEX. In preparation for the congratulatory message from the SAAHIP sector, I embarked on some research of the longstanding relationship between PSSA and SAAHIP. In 1946 the different branches of the South African Pharmacist's association amalgamated and became the PSSA, and in 1957 SAAHIP, a sector of the PSSA was formed. My research and reading took me back to the oldest journal articles that I could obtain from the online South African Pharmacy Journal (SAPJ) portal (2006) and I was also handed a presentation and other archives (2007) from SAAHIP Past President, Dr Andy Gray.

Reading these past publications and information, I was transported on a pharmacy journey. I marvelled at past president's messages and words of encouragement. I chuckled when I read another past president's Forum write-up, where he mused that the hardest part of his Presidency is writing these Forum articles, which was totally relatable. The journey of pharmacy in South Africa was well documented, detailing our positions over the decades, the challenges experienced, and the solutions proposed. It was easy for me to see the evolution that has taken place. It gave me renewed hope, made me feel better equipped as a leader in the current times and highlighted that I am not alone as I am surrounded by these amazing leaders and the wealth of knowledge that they have.

The hospital pharmacy profession has evolved from dispensing to a more clinical approach. We have moved into the pharmaceutical care era, where pharmacists are able to influence medication prescribing, medication administration and overall medication outcomes of the

patient. We are now valued members of the multi-disciplinary team, involved with clinical decisions, able to provide sound drug interaction analysis and medication reconciliation whilst also providing comprehensive counselling for the patients along with efficient health education. We would never have reached these milestones in healthcare if we didn't evolve, improve or learn from the past.

I have often heard we stand on the shoulders of giants in the SAAHIP space and I personally, am incredibly grateful to all the leaders that have come before me. I have also been very intentional in preserving their work and using it as a guiding force or strong foundation for my vision, term and the future of pharmacy. Older practises hold significant value. I encourage you to do similar in your practise. Like the above quote from Einstein, the past is there for us to learn from, if we dwell in it – then we will unfortunately not move forward. If we use it as a foundation and learning block, then we can improve and do better! Pharmacists are resourceful and resilient and have managed to move themselves out of the basements of hospitals, solely responsible for drug supply and procurement to being a valued and trusted clinical member of the healthcare team, advisor and patient care advocates. We truly have been able to learn from the past and seize the current day!

The South African Association of Hospital and Institutional Pharmacists (SAAHIP)
38th Annual Conference and 70th Annual General Meeting

11-13 March 2027

Operation 3i's

Advancing Pharmaceutical Services

innovate, integrate, improve

Conference Announcement

About the SAAHIP Conference

The South African Association of Hospital and Institutional Pharmacists (SAAHIP) hosts an annual conference that brings together hospital and institutional pharmacy personnel to explore the latest advancements in hospital pharmacy practice. This event serves as a platform for hospital and institutional pharmacists and pharmacist assistants to exchange knowledge, share research findings, and discuss emerging trends in medication management, patient safety, and healthcare policy. SAAHIP continues to focus on continuous professional development. The 2027 conference will feature a variety of academic and practice-based podium and poster presentations, pearl presentations, workshops, keynote presentations, and networking opportunities, offering valuable insights into enhancing pharmacy services across South Africa.

Advancing Pharmaceutical Services: Innovate - Integrate - Improve

The Northern Gauteng Branch of SAAHIP is pleased to announce the 2027 conference, where we will explore the evolving role of hospital and institutional pharmacy within South Africa's changing health system landscape. As the country advances towards universal health coverage, new policy directions continue to shape the delivery of pharmaceutical services.

In this evolving policy and regulatory environment, it is imperative for hospital and institutional pharmacists to adapt and lead. This conference will provide a platform to examine how technological advancements, automation, and integrated healthcare systems can enhance patient care, optimise pharmacy practice, and strengthen pharmaceutical services in alignment with emerging national health priorities.

Invitation

We invite researchers, practitioners, and industry experts to submit abstracts that contribute to this critical discourse and help shape the future of hospital and institutional pharmacy in South Africa. Join us as we **Innovate - Integrate - Improve** pharmaceutical services for the betterment of healthcare.

- **When: 11-13 March 2027**
- **Venue: Location to be confirmed at a later date**
- **Theme: OPERATION 3i's - Advancing Pharmaceutical Services: Innovate - Integrate – Improve**
- **Abstract Submission via: https://conference.saahip.org.za/submit-abstract (https://conference.saahip.org.za/submit-abstract)**

The South African Association of Hospital and Institutional Pharmacists (SAAHIP)
38th Annual Conference and 70th Annual General Meeting
11-13 March 2027

Operation 3i's

Advancing Pharmaceutical Services

innovate, integrate, improve

Call for Abstract

The healthcare landscape is undergoing great transformation, driven by rapid technological advancements, evolving healthcare policies, and the increasing need for integrated, patient-centred pharmaceutical services. This landscape brings forth new opportunities for personalised medicine, automation, artificial intelligence, data-driven decision-making, and digital health solutions. As South Africa progresses towards the implementation of the National Health Insurance, hospital and institutional pharmacists must **innovate, integrate, and improve** pharmaceutical services to ensure efficient and effective pharmaceutical care within a restructured healthcare system.

This conference aims to provide a platform for knowledge exchange, discussions, collaborations, and equipping hospital and institutional pharmacy personnel with the insights and tools needed to thrive in this transformative era.

We invite researchers, pharmacy personnel, managers, and thought leaders to submit abstracts (https://conference.saahip.org.za/submit-abstract/) for a podium or poster presentation (academic, scenario, quality improvement project), a pearl presentation and or a workshop/symposia/seminar that contribute to this vital discourse and shape the future of hospital and institutional pharmacies in South Africa.

Abstracts submission: https://conference.saahip.org.za/submit-abstract

Categories for submission of abstracts	
Sub-themes	**Category**
Access to medicines	**Supply chain resilience, medicines availability, logistics and procurement strategies and ensuring equitable access in institutional settings.**
Patient-centred care	**Management and prevention of communicable and non-communicable diseases using strategies such as, but not limited to personalised pharmacotherapy, pharmacogenomics, vaccines, medication adherence and patient counselling.**
Evidence-based practice	**Implementation of clinical guidelines and best practices including real-world evidence and health outcomes research. Analysis of economic evaluations and cost-effectiveness in pharmaceutical care.**
Digital health solutions	**Digital health technologies e.g. tele-pharmacy, mobile applications, and electronic health records, in optimising pharmacy practice.**
Sustainable resource management	**Readiness to thrive in high service-demand environments experiencing resource challenges and workforce inadequacies.**
Legislative readiness	**Current and future strategies to navigate legislation, regulation and policies within the South African context.**

The above sub-themes are by no means an exclusive list. Other topics may be worthy of presentation.

Important Dates	
Description	**Dates**
Abstract submission deadline	30 September 2026
Abstract review	1 October – 30 November 2026
Notification of abstract submission outcome	15 November 2026

Pedagogies of practice: Where knowledge meets action

Mariam Parker (PhD)

School of Pharmacy, University of the Western Cape

Mariam is the recipient of the Distinguished Teacher Award, awarded at the APSSA Conference in 2025.

Pharmacy education occupies a distinctive and demanding pedagogical space. It asks learners to integrate scientific knowledge with regulatory competence, ethical reasoning and human engagement, all within health systems where complexity is routine and certainty is a luxury. Graduates are expected not merely to know, but to decide, communicate, judge and act responsibly in real-world contexts.

Over time, my central emphasis has been how best to design learning environments that support this transition: from theoretical understanding to applied judgement, and from passive recipient of information to accountable practitioner. Through this lens, teaching becomes a form of design: the purposeful crafting of experiences that shape professional identity over time. If practice is where pharmacists are tested, education is where they are tempered.

Teaching philosophy: a pedagogy of becoming

My teaching is guided by a simple organising idea: professional identity is not something we assess at the end; it is something we design for throughout. I draw on constructivist and dialogic learning to build reasoning through interaction.[1] I also draw on critical pedagogy and transformative learning to help students examine assumptions, power and professional responsibility.[2,3] I work with the practical logic of cognitive progression: a curriculum cannot remain lodged at recall and comprehension if the profession demands analysis, evaluation and judgement.[4,5]

Practically, I design learning to be:

- Engaged (how students contribute, connect and are heard)
- Authentic (grounded in real systems and constraints)
- Socially accountable (where dignity and access are pedagogical conditions, not optional extras)

This philosophy has matured into three distinct coordinated commitments, each with its own underpinning rationale: (1) technology-enhanced learning (TEL), to widen participation and cultivate ethical digital fluency in a tech-driven world; (2) experiential learning (EL), as the curriculum's organising logic: structured, scaffolded, quality-assured and accountable to professional regulation and health-system realities; and (3) socially just higher education, designed for uneven schooling histories, variable preparedness and resource-constrained contexts, with a focus on epistemic access and dignity. These strands intersect in practice, but each addresses a different educational problem and therefore has its own underpinning.

Technology-enhanced learning

Students live and learn in a digitally saturated world. The question is not whether technology is present, but whether it is used to deepen learning, widen participation and strengthen professional judgement. I treat TEL as pedagogical infrastructure as opposed to a novelty. Rather than simply modernise delivery of education, it should support learning and ethical leadership.

TEL as a participation architecture

A practical example emerged in post-pandemic reflective components of experiential education. Sessions that had previously been dialogic became muted; many students were more comfortable typing in online spaces than speaking in physical classrooms. Rather than reading this as disengagement, I treated it as an access issue: access to voice. The response was to redesign the participation pathway.

By introducing live interactive platforms (for example, Padlet and Mentimeter accessed via QR codes), students can contribute anonymously in real time, see patterns and tensions emerge on-screen, and then use those themes as a bridge back into spoken discussion. This approach leverages students' preferred access medium while providing structured scaffolding from tentative contribution toward articulated reasoning. Through this lens, TEL is not a "tech add-on". It is engaged participation design, and it makes dialogue visible with a direct link to the professional skill of communicating under conditions of uncertainty.

Generative AI: from policy anxiety to ethical competence

My second emphasis is the ethical and critical integration of generative AI. My approach is non-prohibitionist because blanket bans tend to displace learning into private, unteachable spaces. Instead, I foreground critical digital literacy: capabilities, limitations, bias and

verification practices, paired with transparency and integrity. UNESCO's guidance for generative AI in education emphasises the need for human-centred implementation and explicit teaching of responsible use.[6] Current scholarship similarly cautions that large language models require new literacies including fact-checking, source discipline and clear boundaries between assistance and authorship.[7]

In curriculum terms, this means treating AI as an object of professional reasoning. Students are encouraged to document AI use, retain prompt histories where appropriate, and cite responsibly, thereby making epistemic responsibility visible. This aligns with emerging practical frameworks that treat AI as a learning partner in bounded, declared ways.[8]

Experiential learning: from episodic exposure to structured formation

Experiential learning in pharmacy is often described in aspirational terms as *real-world exposure*. I treat it in the language that makes it sustainable: design, supervision, assessment, coordination and quality assurance. A placement is not automatically a pedagogy; it becomes one when it is *structured, supported* and *assessed.*

Experiential learning in South African pharmacy education is embedded in accreditation requirements and governed through professional standards and guidelines.[9-11] The theoretical underpinning is equally strong. Kolb's experiential learning theory frames learning as a cycle of experience, reflection, conceptualisation and experimentation.[12] In pharmacy education, the instructional challenge is to ensure that experience does not remain episodic, and that reflection is not sentimental. Reflection must function as disciplined sense-making: translating experience into judgement and transferable professional insight.

Avoiding fragmentation: making the trajectory visible

A recurring challenge in longitudinal experiential curricula is fragmentation. Students can experience the programme as hours to accumulate rather than as a coherent developmental trajectory. My response has been to make the pathway legible and to support students in interpreting EL as a scaffolded identity journey. When progression is visible, experiential learning shifts from episodic exposure to sequenced development.

Service-learning and Reciprocity: a South African scholarly lineage

At UWC's School of Pharmacy, service-learning has a strong scholarly lineage. Bheekie and colleagues have shown how service-learning contextualises pharmacy training within the realities of public-sector healthcare and community need, linking student learning to service delivery and social accountability.[13,14] This scholarship matters because it clarifies that reciprocity is not charitable sentiment; it is pedagogical design. It also aligns with work on the hidden curriculum in work-based learning, which reminds us that students learn values, norms and assumptions in practice settings regardless of whether we name them explicitly.[15] Through this lens, EL becomes an epistemic practice that teaches students how knowledge works under constraint, how systems shape decisions and how responsibility travels with the pharmacist into real clinical spaces.

Socially just higher education: dignity, transition, epistemic access

This third strand is not a "values layer" applied only to TEL or EL. It is its own pedagogical commitment: designing higher education that recognises uneven schooling histories and structural inequality as teaching conditions, not student deficits. In South Africa, widening participation is inseparable from epistemic access: not only who enters university, but who gains access to disciplinary ways of knowing and being.[16,17]

In a cognitively demanding programme where many students come from resource-constrained environments, transition challenges can shape both success and belonging. My response is to treat foundational literacies, metacognitive learning strategies and digital academic fluency as part of the core curriculum rather than as outsourced, optional support. When academic literacies are embedded early and taught as disciplinary practices, students gain access to the "how" of academic work. They learn to read strategically, reason with evidence, write with precision and communicate professionally. This is equity enacted as design.

Social justice in my teaching is also practical: access to the tools of modern learning and practice. I therefore make digital competence explicit rather than assumed, including navigating learning platforms and developing professional digital communication. The intention is to surface the hidden curriculum of university learning so that success is not reserved for those who arrive already fluent in institutional codes.

Students' encounters with public healthcare can involve resource scarcity, uneven care and professional tensions. I frame these realities as catalysts for reflection and growth, consistent with transformative learning.[3] The aim is neither naive optimism nor cynicism. It is ethical and analytic capacity: to notice, to name, to reason and to act responsibly within complex systems.

Finally, socially just education in my work includes communication equity. Language barriers and health literacy gaps shape patient safety and dignity; education must respond accordingly. Community-engaged translation and communication initiatives can function as socially accountable scholarship, strengthening students' professional identity while addressing inequity in practice.

Stewarding professional becoming

Receiving the Distinguished Teacher Award has offered an opportunity to reflect on both my personal practice and the collective responsibility of pharmacy educators. Teaching excellence is not achieved through isolated innovation. It is built through sustained, principled design aligned with professional purpose.

As pharmacy education confronts rapid technological change, expanding scopes of practice and rising societal expectations, the more durable question is this: how do our learning designs support the formation of pharmacists who are thoughtful, ethical, adaptable and accountable? I remain convinced that technology-enhanced learning,

experiential education and socially just pedagogy each offer powerful possibilities for shaping pharmacists who can navigate complexity without losing their ethical centre. Whether the entry point is a QR code, a clinic corridor, or a difficult conversation about system failure, the aim remains constant: to design for becoming, so that graduates are equipped not merely to function within existing systems, but to strengthen them.

References

1. Vygotsky LS. Mind in society: The development of higher psychological processes. Cambridge (MA): Harvard University Press; 1978.
2. Freire P. Pedagogy of the oppressed. New York: Continuum; 1970.
3. Mezirow J. Transformative dimensions of adult learning. San Francisco: Jossey-Bass; 1991.
4. Bloom BS. Taxonomy of educational objectives: The classification of educational goals. Handbook I: Cognitive domain. New York: McKay; 1956.
5. Anderson LW, Krathwohl DR, editors. A taxonomy for learning, teaching, and assessing: A revision of Bloom's taxonomy of educational objectives. New York: Longman; 2001.
6. UNESCO. Guidance for generative AI in education and research. Paris: UNESCO; 2023. Available from https://unesdoc.unesco.org/ark:/48223/pf0000386693?locale=en (Accessed 16 January 2026.)
7. Kasneci E, Sessler K, Küchemann S, Bannert M, Dementieva D, Fischer F, et al. ChatGPT for good? On opportunities and challenges of large language models for education. Learn Individ Differ. 2023;103:102274. https://doi.org/10.1016/j.lindif.2023.102274. Available from: https://www.researchgate.net/publication/367541637_ChatGPT_for_Good_On_Opportunities_and_Challenges_of_Large_Language_Models_for_Education Accessed 14 January 2026.
8. Mollick E, Mollick L. Assigning AI: Seven approaches for students, with prompts [preprint]. arXiv. 2023. https://doi.org/10.48550/arXiv.2306.10052 Available from: https://arxiv.org/pdf/2306.10052.pdf Accessed 16 January 2026.
9. South African Pharmacy Council. Good Pharmacy Education Standards (Higher Education and Training) (Board Notice 183 of 2017). Gov Gaz. 17 November 2017;41256. Available from: https://www.gov.za/sites/default/files/gcis_document/201711/41256bn183.pdf (Accessed 16 January 2026.)
10. South African Pharmacy Council. Amendments to Good Pharmacy Education Standards (Higher Education and Training) (Board Notice 32 of 2019). Gov Gaz. 15 March 2019;42304. Available from: https://www.sapc.za.org/Media/Default/Documents/BN32%20of%202019%20-%20Amendments%20to%20Good%20Pharmacy%20Education%20Standards%20-%20HET.pdf (Accessed 16 January 2026.)
11. South African Pharmacy Council. Guidelines for Work-Based Learning (WBL) (Board Notice 816 of 2025). Gov Gaz. 4 August 2025;53112. Available from: https://www.gov.za/sites/default/files/gcis_document/202508/53112bn816.pdf (Accessed 16 January 2026.)
12. Kolb DA. Experiential learning: Experience as the source of learning and development. Englewood Cliffs (NJ): Prentice Hall; 1984.
13. Bheekie A, Adonis TA, Daniels P. Contextualising undergraduate pharmacy training in service-learning at the University of the Western Cape. Educ as Change. 2007;11(3):157-167. https://doi.org/10.1080/16823200709487186.
14. Bheekie A, Obikeze K, Bapoo R, Ebrahim N. Service learning in pharmacy: Opportunities for student learning and service delivery. Afr J Pharm Pharmacol. 2011;5(23):2546-2557.
15. Van Huyssteen M, Bheekie A. The hidden curriculum of work-based learning for pharmacy students in public sector pharmacies in South Africa. Pharm Educ. 2017;17(1):190-198. Available from: https://pharmacyeducation.fip.org/pharmacy-education/article/view/481/435 Accessed 14 January 2026.
16. Morrow W. Bounds of democracy: Epistemological access in higher education. Cape Town: HSRC Press; 2009.
17. Muller J. Every picture tells a story: Epistemological access and knowledge. Educ as Change. 2014;18(2):255-269. DOI: 10.1080/16823206.2014.932256 Available from: https://www.researchgate.net/publication/272121340_Every_picture_tells_a_story_Epistemological_access_and_knowledge Accessed 16 January 2026.

Maintenance and repair of technology,

quality assurance

Efficient cleaning of industrial production plants with dry ice

Whether you are an industrial service provider or part of a production team, effective cleaning of production plants requires technologies that integrate seamlessly into processes and deliver fast results. In times of skilled labour shortages, unproductive steps must be completed as quickly as possible. At the same time, cleanliness is essential for consistent product quality and protecting expensive equipment. Dry ice blasting offers a gentle, efficient method that complements established cleaning routines. A recent innovation now enables the machine to produce dry ice itself, making the process even more flexible and easy to use.

Dry ice blasting:
How the technology works.

Dry ice blasting is a particle stream process using CO_2 pellets measuring 0.5–3 mm as the blasting medium. Unlike conventional abrasives that remain solid during use, dry ice combines mechanical and thermal energy to achieve high cleaning performance. Pellets at –79 °C strike the surface at speeds of up to 150 m/s, releasing kinetic energy. The extreme cold makes contaminants brittle so they detach more easily.

A key effect is sublimation. When the frozen CO_2 hits the surface, it transitions from solid to gas, expanding up to 400 times in volume. This expansion penetrates cracks in dirt layers or coatings, lifting and breaking them apart. Only the removed contaminants remain behind and can be blown away with compressed air or vacuumed up.

Because the method is minimally abrasive and leaves no moisture or blasting residue, it is suitable for sensitive surfaces and areas where water cannot be used. Different nozzle geometries allow adaptation to specific tasks, and pellets can be crushed for especially gentle cleaning.

Blaster, compressor, pellets and co.:
What must be considered in the selection.

Large dry ice blasters for heavy-duty applications consume approximately 30–100 kg of pellets per hour. The system injects pellets into a compressed air stream delivered through a hose, trigger gun and nozzle. Compressed air must meet at least Class 3 (ISO 8573-1), so separators and aftercoolers are recommended.

Traditionally, pellets are produced in hydraulic presses and delivered within 24 hours in many regions. Stored in insulated containers, they remain usable for three to five days. Over time, however, they sublimate, lose density and clump together, reducing performance. Companies with high or continuous demand can produce pellets on site using a pelletiser and liquid CO_2 tank.

A newer solution eliminates pellet logistics altogether. The blaster generates pellets directly during operation in the exact quantity required. Users only need liquid CO_2 cylinders and compressed air. Intuitive controls and monitoring systems make operation straightforward, without lengthy training.

In use:
Advantages for cleaning production plants.

Dry ice blasting effectively removes grease, oils, wax, adhesives, silicone and welding residues. It reduces manual labour and avoids water, chemicals or solvents that may damage sensitive materials or leave residues.

Machines can be cleaned while assembled, minimising downtime and enabling maintenance between production shifts. Injection moulds,

welding robots and automated systems with delicate electronics benefit particularly from this approach. The process also reduces physical strain on operators and eliminates hazardous chemicals, wastewater and abrasive residue. Dislodged dirt can simply be swept or vacuumed away.

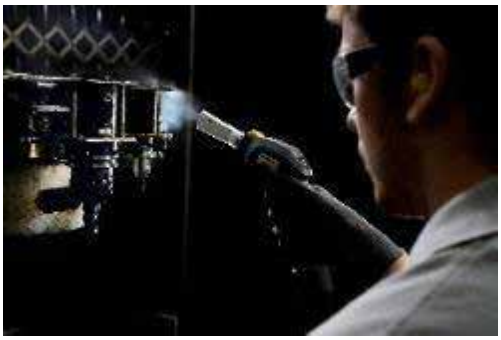
Work protection:

What users must bear in mind (box).

Noise levels range from 75 to 125 dB(A), so hearing protection is required. PPE should include protective clothing, gloves and eye protection to prevent cold burns. Adequate ventilation is essential, as CO_2 concentration must not exceed 0.5 percent by volume. Monitoring devices ensure workplace safety.

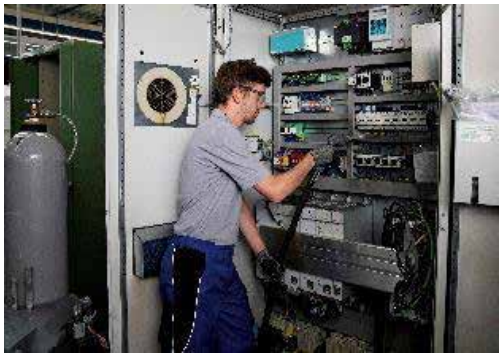
Separating agents and burned-in residue can be removed from plastic injection moulds using dry ice, ...

...so that the quality of the components is assured. The cleaning can take place when the mould is still warm, which leads to short set-up times.



As very narrow areas can also be reached with dry ice, the cleaning of a tool changer is also easily possible. Emulsion, deposits and metal shavings are reliably removed.

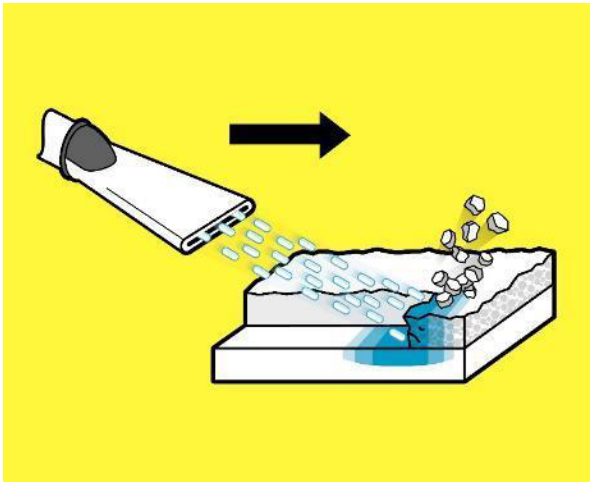
The sensitive filter mats are not damaged by dry ice during the maintenance cleaning of a ventilation system.



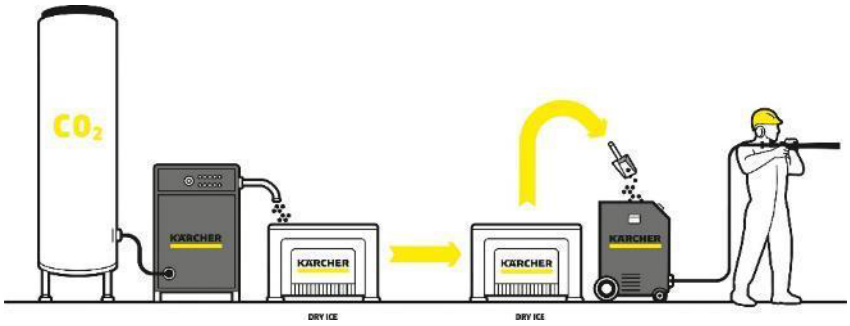
Over the years vapours or dust containing oil may end up in control cabinets and cause malfunctions or even a fire. With dry ice blasting...

...deposits are removed from the sensitive electronic components and contact points gently and without any residues.

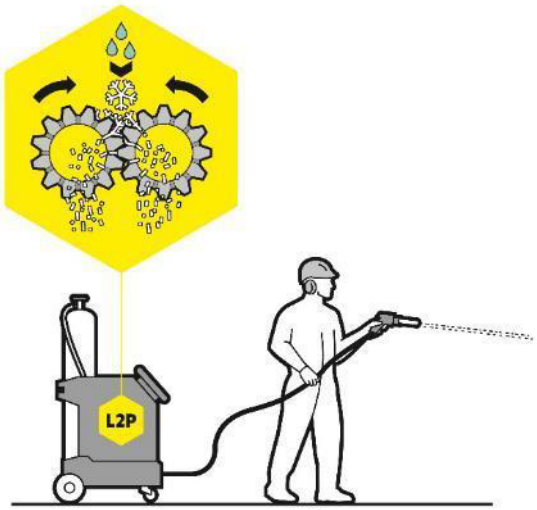
With welding robots traces of powder and welding residue can be easily removed with dry ice.



Dry ice blasting also works through sublimation: Parts of the frozen carbon dioxide penetrate the cracks of dirt crusts or paint applications, go from a solid to a gaseous state and can really break up the dirt thanks to this increase in volume.



Systems which are supplied with dry ice pellets are available on the market as well as...



...a compact model which produces the dry ice itself and therefore can be used very flexibly.

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Lenacapavir in HIV prevention care: What the pharmacist should know	
1.	**Which viral structure is targeted by lenacapavir?**
a	Reverse transcriptase
b	Integrase enzyme
c	Capsid protein (p24)
d	Envelope glycoprotein
2.	**Why is lenacapavir effective against multidrug-resistant HIV-1?**
a	It enhances the immune response against HIV
b	It targets a highly conserved structural protein involved in multiple replication stages
c	It increases the metabolism of other antiretrovirals
d	It blocks viral entry into host cells only
3.	**A patient receiving lenacapavir is also prescribed rifampicin for tuberculosis. What is the most appropriate action?**
a	Avoid co-administration due to reduced lenacapavir levels
b	Continue both medications without adjustment
c	Increase the dose of lenacapavir
d	Administer lenacapavir more frequently
Beyond energy boosts: A clinical review of the vitamin B complex and associated supplementation	
4.	**Which property of the vitamin B complex best explains why toxicity is generally uncommon?**
a	High lipid solubility
b	Extensive hepatic storage
c	Renal excretion due to water solubility
d	Irreversible protein binding
5.	**Why are combination vitamin B supplements commonly used rather than single-vitamin formulations?**
a	Cost-effective design
b	Higher toxicity thresholds
c	Improved gastrointestinal absorption
d	Vitamin B deficiencies coexist
6.	**Why must vitamin B complex vitamins be regularly obtained from the diet?**
a	Rapid deactivation through metabolism
b	No endogenous synthesis and low storage capacity
c	Poor absorption from the gastrointestinal tract
d	Extensive complexation with microbiota

The use of creatine in adolescents	
7.	**Which of the following best describes the primary mechanism by which creatine enhances performance?**
a	Increases oxygen delivery to skeletal muscle
b	Enhances ATP regeneration through the phosphocreatine system
c	Stimulates insulin secretion
d	Reduces lactic acid production
8.	**Which statement regarding the safety of creatine supplementation in adolescents is most accurate?**
a	Creatine is associated with clinically significant renal dysfunction in healthy individuals
b	Creatine consistently causes dehydration and heat-related illness
c	Creatine is generally well tolerated when used appropriately
d	Creatine is contraindicated in all adolescents
9.	**Creatine supplementation is most effective in which of the following types of activity?**
a	Long-duration endurance activities such as marathon running
b	Low-intensity aerobic exercise such as walking
c	Flexibility-based activities such as yoga
d	Short-duration, high-intensity activities such as resistance training
Human papillomavirus in cancer: pathogenesis and vaccination approaches	
10.	**Which high-risk HPV strains are responsible for the majority of HPV-related cancers?**
a	HPV-6 and HPV-11
b	HPV-16 and HPV-18
c	HPV-31 and HPV-33
d	HPV-52 and HPV-58
e	HPV-1 and HPV-2
11.	**Which host tumour suppressor proteins are targeted by the viral oncoproteins E6 and E7?**
a	BRCA1 and BRCA2
b	HER2 and EGFR
c	p53 and pRb
d	MYC and RASB
e	PTEN and APC

12.	**Persistent infection with high-risk HPV can lead to which of the following cancers?**
a	Cervical and oropharyngeal cancers
b	Pancreatic and liver cancers
c	Prostate and bladder cancers
d	Thyroid and adrenal cancers
e	Melanoma and basal cell carcinoma

Dry eye disease management: the pharmacist as first-line health professional

13.	**Dry eye disease (DED) is primarily characterised by which of the following pathological features?**
a	Increased tear viscosity and bacterial colonisation
b	Tear film instability, hyperosmolarity, inflammation, and neurosensory abnormalities
c	Excessive tear production with lacrimal gland hypertrophy
d	Retinal inflammation leading to blurred vision
14.	**Which of the following diagnostic findings is most suggestive of tear film instability in dry eye disease?**
a	Tear break-up time (TBUT) greater than 15 seconds
b	Schirmer test value greater than 15 mm
c	Increased intraocular pressure
d	Tear break-up time (TBUT) less than 10 seconds
15.	**How are autologous serum eye drops (SEDs) correctly prepared?**
a	Blood is collected with anticoagulants and stored at room temperature
b	Blood is collected without anticoagulants, clotted, diluted in saline, and frozen
c	Serum is concentrated from donor plasma through evaporation
d	Blood is mixed with artificial tears and stored in one large container
16.	**As a first line contact, what is the pharmacist's role in managing dry eye disease?**
a	Performing objective diagnostic tests like the Schirmer test or tear osmolarity testing
b	Carrying out surgical interventions such as punctal cautery or amniotic membrane grafting
c	Differentiating DED from other conditions like allergic eye disease, recommending appropriate over-the-counter treatments and educating patients on lifestyle modifications
d	Restricting treatment to the dispensing of prescription-only topical corticosteroids

Overcoming vaccine hesitancy: An effective vaccine communication 'standard operating procedure' for pharmacists

17.	**The following statement is TRUE:**
a	The world is on track for reaching the WHO Immunization Agenda 2030 goals
b	Measles has once again become endemic in the USA
c	South Africa has recently experienced diphtheria outbreaks
d	Infant vaccine coverage in South Africa has been improving over the past two decades
18.	**Vaccine hesitancy …**
a	is a relatively modern phenomenon, originating in the late 20th century
b	includes vaccine denial, which responds well to behavioural interventions
c	is a state of indecision and uncertainty about whether or not to vaccinate
d	cannot be addressed in the age of social media-driven mis/disinformation campaigns
19.	**When you notice your infant patient has missed their scheduled routine vaccinations, your first reaction should be to …**
a	ask their caregiver what they think about getting their infant vaccinated today
b	admonish their caregiver for missing their infant's scheduled vaccinations
c	ask their caregiver why they missed their infant's scheduled vaccinations
d	tell their caregiver that their infant is due for vaccination catch-up today
20.	**When a caregiver is reluctant to have their infant vaccinated, you should …**
a	show them pictures of a child severely affected by a vaccine-preventable disease, and warn them that they are putting their child at risk for this type of outcome
b	gently enquire why they are reluctant, and listen patiently while they explain
c	focus on appealing to their sense of social responsibility by stressing the importance of vaccination as a 'collective good' that results in herd immunity
d	tell them all about the vaccine myths you have seen on the internet and social media, and then explain why these myths are untrue

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 2 • 2026

1. b 2. c 3. b 4. c 5. c 6. b 7. b 8. a 9. b 10. c 11. b

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