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1. Glentriz™ Approved Professional Information. January 2021.
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3. Data on file.

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**ADVERTISING SALES**
Sandy Laranja (Medpharm)
Cell: 082 853 4155
E-mail: sandy@medpharm.co.za

**SUBSCRIPTION**
info@medpharm.co.za

**PUBLISHER**
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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,
Ground Floor, Centurion Wine & Art Centre,
123 Amkor Road, Lyttelton Manor
PO Box 14804, Lyttelton, 0157
Tel: (012) 664-7460, Fax: (012) 664-6276
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# contents

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## 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.

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|---|---|
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# A Piece of my Mind

Editorial Comment

## Should I or shouldn't I?

I started thinking about the way that I relate to people has changed over the years, and particularly within the working context. Naturally, I transferred my thoughts into writing – old habits die hard. Should I publish it as *A Piece of my Mind*? Is it relevant to your practice, or is it just part of my personal journey? We all have our own personal journeys, but the past 22 months have shown us that there's often a lot of overlap. We usually don't talk about it, but maybe I should share my personal work communication experience – maybe it will ring a bell.

## Going back to basics

I've been reflecting on the way my working preferences changed over the years. When I was 17 years old, I finished school (where the only extramural activity that I'd enjoyed had been the debating society) and went straight to work in a clinical microbiology laboratory. In those days, you worked during the day, and went to the Tech three nights a week. My physiology lecturer was a young man, who became my significant other 44 years later – thank goodness I passed physiology that year.

I loved working in the lab but I volunteered for evening shifts and public holidays when I worked on my own with the pathologist. I much preferred that to working with other people – at least I didn't have to talk to them.

I also discovered that I got highly irritated when phoning doctors with urinary microscopic, culture and sensitivity results – especially the one who commented, "Oh, so THAT's why my wife isn't responding to the antibiotic I gave her!". I'm glad I was never his patient.

## And then I discovered flowers

My parents decided to buy a florist shop, so I qualified as a florist. This was in the olden days when natural was unnatural and flowers needed to do as you wanted them to do. Quite a challenge. During my final exam, I was working on an intricate wedding bouquet and, while I prepared something to put in it, I let the work in progress hang from a Coke bottle so that I had both hands free. Imagine how I felt when I realised that some low hanging flowers had landed in a cup of coffee next to the Coke bottle! Quick repair work needed there!

In that job, we worked with people, but flowers usually make people happy. Yes, there were the funeral flowers, but hopefully, they brought some peace and tranquillity to those who were grieving a loss. On the evenings before Mother's Day and Christmas Day, my mom and I seldom got home before midnight. Our drivers needed to go home early, so we carried on with deliveries. And the recipients always appreciated it.

## Students are nicer than people!

Ten years after leaving school, I eventually realised that I wanted to study pharmacy, and despite being constantly anxious, I really enjoyed it – all those fairy tales, especially organic chemistry. And I'm still in awe that my electrons may be roaming around in a different room from me! (Can I trust them there?)

It was fairly inevitable that, after my internship in community pharmacy, I would end up in academia. The people I met in community pharmacy didn't want to be there – they were ill, and felt miserable and irritable. So when I met students, it was such a pleasure. I really enjoyed their enthusiasm. Most of them really wanted to enter the profession. Compared to dealing with "customers", interacting with students was an absolute pleasure. And it still is. They WANT to make things work!

## Working in regulatory pharmacy

When I left Wits, I worked for a short while in animal health product registration. I thought I would enjoy it because there would be minimal contact with other people and lots of reading. I'm afraid it was about 30 years too early for me. I sourced all information, including site master plans, via email from Ireland and France, but the MCC insisted on pieces of paper, so I sat staring at files and piles of paper covering the walls of my office, I really didn't understand why the information couldn't be communicated electronically. Maybe I'd enjoy it more nowadays.

## Next stop – the PSSA!

I learned that one communication style does not fit all! Phones never stop ringing – pharmacists, consumers, regulators. And then there is the SAPJ, so along come authors and readers and advertisers. Most of them also use email, and to my lasting embarrassment and irritation, I just never managed (then or now) to keep up with them.

Don't get me started on meetings, either. I'm exhausted just thinking about them. International meetings were fun though – you generally needed to speak slowly and enunciate every word clearly because many participants were not English speakers. I remember an earnest conversation I had with one delegate at a conference in Portugal. We both spoke slowly and clearly, until I realised that he was American and his home language was (apparently) English so we could actually speak normally to each other! At least we had a good laugh about our initial conversation.

## Media relations

What a challenge! Especially in the early days of the pricing regulations. I could write a thesis on this! Let me just say that I learned a lot. For example, a live broadcast is better than a pre-recorded one – your

words can't be distorted during editing! Always have an opinion and a message – "no comment" doesn't help to build useful relationships.

## The SAPJ

I think I finally found a communication style that suits me – I enjoy reading and writing. At times, my time management skills might be a bit lacking, but I love the SAPJ and the Medpharm team behind it. And thank you, PSSA, for letting me continue with it after retirement.

## Hospital pharmacy

For many years, I worked part-time in hospital pharmacy. Funnily enough, I didn't mind communicating there – it was mostly unemotional and factual discussions with nurses or doctors. I can cope with that. I could even cope with disagreements with them – I would much rather argue with a nurse or a doctor than have conflict with a consumer in a community pharmacy!

## And then came COVID-19

How has COVID-19 affected your relationships with people? At work? At home? I think I've basically turned into a recluse. I'd be interested in hearing of your experience in maintaining communication skills.

**Lorraine Osman**

# President's Message

# Pharmacy crossing the Rubicon

**Joggie Hattingh**
PSSA President

**Rubicon** refers to a point of no return, going back to Julius Caesar when he crossed the Rubicon river with his army and started a civil war in 50 BCE. Should he have decided to turn back after he crossed the Rubicon river, the decision would have been null and void, as crossing the river set reactions and consequences in motion that could not be reversed.

To my mind, pharmacy has passed a number of Rubicons over the past few years, such as the introduction of minimum standards in pharmacy practice and the introduction of qualified pharmacy support personnel. Some colleagues saw these as challenges or even as threats to the pharmacist, whilst others embraced it as a means to improve service delivery to patients.

Another Rubicon looming on the horizon is certainly the mechanisation of stockholding and dispensing units. Again, some of us are sceptical or downright scared of the looming change.

Does this mean the pharmacist has become redundant, will the dispensing unit replace many pharmacist positions in the workplace? More relevant to our theme, has the "Secundum Artem" of our profession also become redundant?

***Secundum Artem*** means "according to the art". In pharmacy, it is often referred to as the compounding of medicine for the complex patient with a specific need, using the pharmacist's special skill and judgement. (Kobus le Roux, Past President of CPS)

We have long since passed the time where compounding is done for every individual patient, as part of everyday practice, although this art is still practised by a small number of "compounding pharmacists".

As for the position of the pharmacist, I can say with certainty that no pharmacist should lose their position due to mechanisation of community or hospital pharmacy, unless they are themselves guilty of making their skill set redundant. What I'm trying to bring home is that by not keeping abreast of the latest developments in our field of practice, our skill set may well become outdated! Therefore, do not treat CPD like the enemy, but make it your friend!

Many pharmacists who have installed dispensing units in their pharmacies, reported that due to the fact that they have much more time to properly consult with patients, their pharmacies have become much busier and they actually require more pharmacists! How many of us have taken up the challenge to obtain a Primary Care Drug Therapy (PCDT) qualification or immunisation and who intends to do the Pharmacist Initiated Management of Anti-Retroviral Therapy (PIMART) qualification? These are skills that will make any pharmacist a great asset for employers and patients.

Is the "Secundum Artem" segment of our profession dead because we no longer compound for the individual? Certainly not! Who is better qualified to work out correct treatment regimens for the "difficult" patient who has multiple comorbidities and who can best determine the relevance of possible contraindications, drug-drug interactions, drug-food interactions and drug-disease interactions than the pharmacist? This function must be performed by the pharmacist in public sector pharmacies, corporate pharmacies and in privately owned pharmacies, irrespective of who the owner is. Patients need to be listened to, their fears must be heard and addressed, and they must be advised! I dare say that the better this is done, the busier the pharmacy will be!

Pharmacists need to be part of the decision-making team when it comes to developing a treatment plan for patients, together with the doctor, nursing staff and auxiliary health personnel. Why are pharmacists still afraid to engage with the rest of the health team? I see some very young pharmacists taking up this role with aplomb and they are accepted by the rest of the health team without question.

This is the new "Secundum Artem" for pharmacy! Are we ready to practise "according to the art"?

Another Rubicon we have to cross is Universal Health Access. As I have mentioned on many occasions: We (as a profession) can either determine the role of the pharmacist in Universal Health Access or allow someone else to do so.

Universal Health Access is not going to disappear like the last two health ministers did; it is here to stay. We can close our eyes and ignore it, or we can shape its format to best suit us. Many of us saw the COVID-19 pandemic as the ideal platform for the National Department of Health (NDoH) to prove to us that the country's health sector has turned the tide with regards to fraud and corruption. What a rude awakening we had!

Admittedly I was (and I still am) outspoken about the challenges Government will face to get buy-in for Universal Health Access from healthcare professionals, subsequent to the spectacular failure to

control COVID-19 funding (I refer to the "Message from the President; SAPJ October 2020 – To trust or not to trust"), but our concerns will not stem the tide of the incoming Universal Health Access. We need to work with Government to develop a system that will ensure equitable access, good governance, fair reward for services rendered and finally to ensure that private enterprise can still flourish.

How we do this is in your hands! You can inform the leadership of the profession and of the country of what you would like to see, how you see it work, what would be acceptable and what not, etc. But if you do not act and if you do not interact with your representatives on the different fora, the system will be developed without your input.

The Rubicon is upon us!

The choice is yours!

I wish all our colleagues a restful and invigorating festive season, may you enjoy a happy festive season, with love, health, and peace in abundance.

To those who observe Christmas, may you experience God's love and blessing in abundance this Christmas.

## Independent Pharmacy Emergency Relief Fund (IPEF)

In the September/October issue of the SAPJ, the PSSA discussed the looting of pharmacies and the relief fund that ICPA established to assist independent pharmacies that had been looted to become operational again.

The PSSA National Executive Committee agreed that in light of the recent unrests and turmoil in our country that have severely affected some of our members, the PSSA would like to join hands in supporting the emergency fund initiative. The PSSA is assured that the funds will be managed according to robust procedures and distributed fairly since PSSA National Office Executive Director, Ivan Kotzé, serves on the disbursement committee and PSSA staff member, Mariet Eksteen, is the project manager for IPEF.

To show support to the individual pharmacies and the communities they serve, it was proposed that the PSSA contribute R1 million to the emergency fund. The Financial and Human Resource Committee and the National Executive Committee have unanimously supported the proposal.

Even though the help is for a small section of the profession (independently owned pharmacies in two provinces), it goes to the profession's heart. Some colleagues have lost so much, and it happened almost overnight. The destroyed corporate pharmacies have the back-up of their companies and salaries, etc., were paid, whereas the privately-owned pharmacies simply do not have this backing. If corporate colleagues were in the same situation, the PSSA would have requested the same for them. The affected professionals have lost their means to serve the communities that they have served for many years. The PSSA feels that this contribution isn't just a benefit to the pharmacists but indirectly also benefits the patients served by these pharmacies.

These events do not occur frequently, and the devastation and destruction were felt throughout our whole country.

The PSSA is a robust society and well recognised in our profession and beyond. The PSSA is well respected and has set an example for our stakeholders in the pharmaceutical industry. It is time to give back to our members! We challenge others to give boldly too.

The KwaZulu-Natal Inland Branch of the PSSA also contributed R20 000 to the IPEF. The branch is small and their communities were hard hit during the unrests, so it is heartening that they could manage to support their colleagues during these difficult times.

***Let's be bold and generous because we have much for which to be thankful.***

## PIMART

The South African Pharmacy Council (SAPC) on 22 March 2021 published Board Notice 17 of 2021 for comment. The board notice contained the proposed scope of practice of pharmacists who provide Pharmacist Initiated Management of Antiretroviral Therapy (PIMART) services, the competency standards of such pharmacists and the proposed criteria for the approval of a curriculum of a PIMART course. The closing date for comments on this board notice was 21 May 2021.

The SAPC also published Board Notice 71 of 2021 on 9 July 2021 for comment and comments closed on 9 September 2021. The board notice contained the GPP Minimum Standards for sexual and reproductive health, which included PIMART.

The SAPC only received two sets of comments on Board Notice 17 of 2021, and on 13 August 2021, Board Notice 101 of 2021 was published for implementation. Some of the medical profession members were outraged by the implementation of PIMART, insinuating pharmacists are not sufficiently trained to diagnose, treat and counsel patients. Since the beginning of the profession, pharmacists have diagnosed and treated patients with Pharmacist Initiated Therapy (PIT) and the Primary Care Drug Therapy (PCDT) pharmacist, which has been around for many years in South Africa, is based on diagnosing and treating patients. Counselling patients is one of the major components of pharmacists' everyday work, and we are the experts on pharmacology.

The members of the medical profession that were upset by PIMART lobbied very loudly in the media and with the Minister and Deputy Minister of Health to retract the legislation. Various strong-worded letters were written to the NDoH and SAPC opposing PIMART. It was encouraging to see how hard the SAPC fought back on this matter, standing their ground that pharmacists are more than competent to complete the PIMART course developed in large by the Southern African HIV Clinicians Society (SAHCS) and then be able to provide PIMART services once they have been granted a Section 22A(15) permit.

It was clear from some of the letters that the individuals who wrote the letters did not read the board notices properly. They combined the information from the PIMART implementation board notice and the minimum standards for sexual and reproductive health board notice. It seems they were under the impression that pharmacists would be inserting intra-uterine devices (IUDs) and provide abortion services. There is no intention that pharmacists would ever be allowed to provide such services as this would fall outside of our scope of practice and training. But oral and injectable contraception does fall within our scope and practice once supplementary training in contraception has been completed.

The PSSA sent a long letter to the Minister and Deputy Minister of Health to support the SAPC in proving that pharmacists are competent enough to provide PIMART services if they have completed the required training. To date, no further communication on this matter has been received. The PSSA will keep members informed of any developments via the PSSA Newsletters.

# PSSA letter to the Minister and Deputy Minister of Health

Dear Dr Phaahla and Dr Dhlomo

## CONCERNS OF MEDICAL PROFESSION AGAINST PIMART

The Pharmaceutical Society of South Africa (PSSA) is shocked by the severe opposition from certain members of the medical profession against the implementation of Pharmacist Initiated Management of Antiretroviral Therapy (PIMART). This opposition is only in the medical profession's interest and not of the public of South Africa, who suffer the most under the HIV epidemic.

## The HIV epidemic in South Africa

South Africa has the biggest HIV epidemic in the world. The Department of Statistics South Africa (Stats SA) released their 2021 mid-year population statistics which estimates that 8,23 million people in South Africa live with HIV.[1]

The National Strategic Plan (NSP) for HIV, TB and STIs 2017 – 2022 in the foreword states that: *This NSP is a clear demonstration of the outstanding progress we have made. It is also a stark reminder of how far we still need to go. Importantly, it provides an excellent illustration of what South Africans can achieve when working together towards the realisation of a shared objective.*" [2] The NSP has eight goals and in the mid-term review[3] of the NSP, it was clear that a large proportion of the goals were not achieved to the level anticipated. Goal 1 of the NSP is explicitly to reduce the number of new infections from 270 000 in 2016 to under 100 000 by 2022. The 2018/2019 target was a 66% reduction from baseline but only a 36% reduction from baseline was achieved.

The NSP talks to the 90-90-90 targets set by UNAIDS for December 2022. In the mid-term review, South Africa achieved 90-68-88. This clearly shows that South Africa is doing well in testing the population, as 90% know their HIV status. However, we are currently only retaining about 68% of patients that are on ARTs. And this is an area where much work still needs to be done.

The implementation of PIMART can go a long way in assisting the country in reaching the second '90'. Pharmacists often see their patients monthly and can regularly discuss concerns, side-effects, and compliance issues with patients. Patients do not have to make an appointment to see a pharmacist. Private sector pharmacies are often open after hours and over weekends and public holidays, making them more accessible to people who must work during the week.

One of the most vulnerable populations currently in terms of new HIV infections are adolescent girls and young women in the age group 15-24, and this population is where access to pre-exposure prophylaxis (PrEP) could play a significant role in preventing new HIV infections, which has a ripple effect on other populations. Pharmacies could be more accessible to these populations without the risk of exposure or stigmatisation as they can visit the pharmacy to buy other medication or necessities and obtain PIMART services.

## Legal considerations

Any legal concerns noted regarding the implementation of PIMART would be unfounded, as a pharmacist would have to apply for a permit from the Director-General of Health in terms of Section 22A(15) of the Medicines and Related Substances Act (Act 101 of 1965)[4] which states that: "*Notwithstanding anything to the contrary contained in this section, the Director-General may, after consultation with the South African Pharmacy Council as referred to in section 2 of the Pharmacy Act, 1974 (Act No. 53 of 1974), issue a permit to any person or organisation performing a health service, authorising such person or organisation to acquire, possess, use or supply any specified Schedule 1, Schedule 2, Schedule 3, Schedule 4 or Schedule 5 substance, and such permit shall be subject to such conditions as the Director-General may determine*." Co-incidentally Section 22C is used to authorise medical professionals and nurses to dispense – thus "encroaching" on the scope of profession and scope of practice of pharmacists to quote the medical profession. Furthermore, the dispensing course is registered at NQF level 6, while the PIMART qualification is registered at NQF level 8,[5] which proves that the course is of a sufficiently high quality to warrant the issuing of a permit for the provision of PIMART services by qualifying pharmacists.

The medical profession raises concerns in terms of Section 39 of the Health Professions Act (Act 56 of 1974)[6] that states: *"Prohibition of performance of certain acts by unregistered persons deemed to pertain to health professions registrable in terms of this Act*

*(1) No person shall perform any act deemed to be an act pertaining to any health profession as may be prescribed under this Act unless he or she-*

*(a) is registered in terms of this Act in respect of such profession;*

*(b) (i) is registered in terms of this Act in respect of any other profession referred to in section 33 to which such act is also deemed to pertain; or*

*(ii) practises a health profession in respect of which the registrar in terms of this Act keeps a register and such act is deemed to be an act which also pertains to such profession;*

*(e) is registered or enrolled as a nurse under the Nursing Act, 1978 (Act No. 50 of 1978), and such act is an act which also pertains to the profession of a nurse.*

The fact that pharmacists are not specifically mentioned in the Health Professions Act does not preclude them from performing any of the functions defined in the Pharmacy Act (Act 53 of 1974) since the Health Professions Act does not have any jurisdiction over the pharmacy profession. The pharmacy profession is legislated in the Pharmacy Act and the relevant regulations to the Pharmacy Act. The Pharmacy Act also allows for establishing the South Africa Pharmacy Council (SAPC), the exact equivalent of the Health Professions Council of South Africa (HPCSA). A narrow approach can therefore not be taken, and all relevant Acts need to be considered.

Furthermore, the narrow interpretation of the medical professional associations of the law brings into question then the legal standing of Nurse Initiated Management of Antiretroviral Treatment (NIMART) since PIMART and NIMART are based on the same principles. NIMART has been accepted practice since 2010 and has not been challenged legally.

## Competencies and skills set of pharmacists to provide PIMART

The claims of the medical profession that pharmacists are not qualified enough to provide PIMART services shows their lack of understanding of the BPharm degree and the pharmacy profession. A pharmacist studies for four years to obtain a BPharm degree accredited by the South African Qualifications Authority (SAQA) on an NQF level 8. Graduates have to complete one year of internship, write a pre-registration examination, and compile a portfolio of evidence of competency during the year, before registration as a pharmacist. The SAPC has published updated competency standards for pharmacists in 2018.[7] "*The competency standards have been developed to encompass the changes and developments in all sectors of pharmacy and practice, including new technologies, work processes, changes in legislation and international trends,* ***primarily to ensure public safety***." According to the standard: *"A competency (plural competencies) represents the individual qualities or attributes of professional activity, the how of performance. These are learned behaviours and are thus able to be effectively incorporated into developmental programmes that require practitioners to apply learned behaviours. Since competency standards are developed with a focus on performance, they facilitate identification of the aspects of performance in the workplace and provide the best means to deduce professional competence. Competency is a broad concept that includes all aspects of practice.*"

The 2018 competency standards for pharmacists consider various development processes. They are applicable when a person is registered as a pharmacist and can practice independently, i.e., from the first year after internship. The competency standards have been developed with three levels of behavioural statements linked to each competency to guide pharmacists in progressing from one level of practice to another.

The three levels are:

(a) Entry level into practice: generally recognised as the first three years of practice

(b) Intermediate practice: generally recognised as between three and seven years of practice

(c) Advanced practice: generally recognised as more than seven years of practice

Some of the competencies that pharmacists must meet, regardless, relate specifically to the provision of PIMART. The primary domain worth noting is 'Domain 2: Safe and rational use of medicines and medical devices', and more specifically, competency standards indicated in the table below as differentiated between the three levels of practice

| Competencies | Item No | Entry level practice | Intermediate practice | Advanced practice |
|---|---|---|---|---|
| 2.1 Patient consultation | 2.1.4 | 2.1.4.1 Identify the need for further information and/or referral to an appropriate healthcare provider/resource | 2.1.4.2 Implement protocols for referral in consultation with other members of the healthcare team | 2.1.4.3 Develop and review protocols for referral in consultation with other members of the healthcare team |
| | 2.1.6 | 2.1.6.1 Where applicable, examine patient records to obtain patient medication and disease history | 2.1.6.2 Implement care plans based on patient records | 2.1.6.3 Develop and review a care plan based on patient records and monitor patient outcomes |
| 2.2. Patient counselling | 2.2.4 | 2.2.4.1 Use an appropriate counselling plan based on patient needs and ensure the safe and effective use of medicine | 2.2.4.2 Respond appropriately to more challenging or complex scenarios requiring patient counselling | 2.2.4.3 Develop and review counselling plan templates to ensure the safe and effective use of medicine |
| 2.3 Patient medicine review and management | 2.3.3 | 2.3.3.1 Liaise with the prescriber or other healthcare professionals to ensure the optimal use of medicines | 2.3.3.2 Liaise with the prescriber or other healthcare professionals to implement a plan to ensure the optimal use of medicines | 2.3.3.3 Contribute to strategies to optimise patient medication management using clinical tools where appropriate |
| | 2.3.4 | 2.3.4.1 Use appropriate protocols to ensure cost-effective use of medicines and medical devices | 2.3.4.2 Use appropriate protocols to ensure cost-effective use of medicines and medical devices | 2.3.4.3 Develop protocols to ensure the cost-effective use of medicines and medical devices |
| 2.5 Therapeutic outcome monitoring | 2.5.1 | 2.5.1.1 Monitor therapeutic outcomes | 2.5.1.2 Monitor and optimise therapeutic outcomes for more complex scenarios | 2.5.1.3 Ensure that protocols are in place to support the optimisation of therapeutic outcomes by pharmacists |
| | 2.5.2 | 2.5.2.1 Consult with other healthcare professionals to optimise therapeutic outcomes | 2.5.2.2 Contribute to the PTC or at formulary design level to optimise therapeutic outcomes | 2.5.2.3 Participate in optimisation of therapeutic outcomes at PTC/formulary design level |

## PIMART relation to NIMART

PIMART is not a world-first (unfortunately, it would have been something to be proud of). NIMART was the world first – one that was lauded by the World Health Organization (WHO) and others worldwide. It is a well-known fact that NIMART has been the cornerstone of the fight against the HIV epidemic in South Africa. The NIMART course has been developed as a response to the call to action by the South African Government to strengthen the response to HIV and TB epidemics and is specifically developed for and aimed at professional nurses working in the field of HIV and TB. NIMART improves the effectiveness of HIV programmes in primary health settings. The 5-day course is a standalone intensive course that focuses on the management of TB, HIV and STIs as well as strengthening counselling skills, monitoring and evaluation of HIV and TB programmes.[8]

A lot of the successes in South Africa can be attributed to the implementation of NIMART. PIMART is everything NIMART is, only with expanded accessibility. A study published in 2013 in the South African Medical Journal (SAMJ) analyses whether the NIMART roll-out to primary healthcare facilities increases access to antiretrovirals in Johannesburg. The authors[9] concluded that "*In order to promote accessibility of ART services, there is need to decentralise services to PHCs through training and mentoring professional nurses in ART initiation. ARV initiation of non-complicated cases at PHCs will reduce the workload of referral hospitals, enabling them to concentrate on complicated cases. It is important to capacitate nurses to integrate HIV services in order to maximise the limited human resources and provide a comprehensive package of care at PHC level. To ensure sustainability of NIMART, partnership with DoH/CoJ partners in mentoring should be prioritised.*" PIMART applies the same principles as it allows for testing, counselling, and initiating **first-line** ART treatment.

PIMART is in line with international and NDoH antiretroviral guidelines. The programme including the treatment algorithm, training, and the referral programme, has been carefully conceived using South Africa's most respected HIV specialists and clinicians. All aspects are tightly controlled and regulated and is based on a strong referral and support system. Therefore it could be deduced that PIMART would have the same beneficial outcomes on the healthcare system that is suffering under limited human resources.

## Moving towards NHI and multi-disciplinary teams

It is clear from their objections that some medical professionals are not open to multi-disciplinary teams working together in the patient's best interest. South Africa is looking at introducing National Health Insurance (NHI) to improve the quality of life for all citizens, heal the divisions of the past, and establish a society based on democratic values, social justice, and fundamental human rights. A big part of the success of the NHI Bill (Bill 11 of 2019) once it becomes legislation will depend on multi-disciplinary health care teams working together. One profession cannot demand a more significant part of the pie than the others for the sake of monetary gain. The NHI Bill[10] defines primary health care as "*means addressing the main health problems in the community through providing promotive, preventive, curative and rehabilitative services and—*

*(a) is the first level of contact of individuals, the family and community with the national health system, **bringing health care as close as possible to where people live and work**, and constitutes the first element of a continuing health care process; and*

*(b) in the public health sector, is the clinic, and in the private health sector, is the general practitioner, primary care nursing professional, primary care dental professional and primary allied health professional, **through multi-disciplinary practices**;".*

PIMART aims to achieve precisely the above – bringing access to the initiation and management of Antiretroviral Therapy Services as close as possible to where people live and work through multi-disciplinary practices. There is a vital referral component in PIMART.

One of the biggest successes of the COVID-19 vaccine roll-out in South Africa has been the multi-disciplinary collaboration between especially pharmacists and nurses. Most of the COVID-19 vaccine roll-out sites in South Africa are run and managed by multi-disciplinary teams working in collaboration in the public's best interest.

## Conclusion

Various letters drafted by medical professional associations have been circulated on the PIMART issue.

As Professor Francois Venter (a world-renown HIV clinician) has said in his letter to SAMA: "*These complaints all mischaracterise the programme to some degree, including untrue claims it includes pharmacists performing abortion care. Several letters contain basic clinical errors in modern HIV care out of step with South African (DoH and SAHCS guidelines for the private sector), as well as international guidelines. Some letters characterise the programme as an over-the-counter conversation, which is grossly misleading (there are strict requirements around facilities and confidentiality). These mis-characterisations undermine patients' rights to accessible therapy.*"[11]

The PSSA is firmly of the opinion that pharmacists are more than qualified to perform PIMART safely and adequately once they have completed the PIMART course. The implementation of PIMART would be to the benefit of the patients and will assist the country in achieving the 90-90-90 targets. If the pharmacists and medical professionals could work together on this, it could be to the advantage of everyone involved.

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# The PSSA/Alpha Pharm distance learning programme 2021

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

## Module 5 – Hypertension update

Raised blood pressure (BP) or hypertension remains a leading cause of death globally. It is the most common condition seen in primary care and leads to myocardial infarction (heart attack), stroke, heart failure, renal failure and death if not detected early and treated appropriately.

According to the World Health Organization, an estimated 1.28 billion adults aged 30–79 years worldwide have hypertension. However, trends show a clear shift from high-income to low- and middle-income countries, with an estimated 349 million people with hypertension in high-income countries and 1.04 billion in low- and middle-income countries.

Despite the high prevalence, hypertension awareness, treatment and BP control are low worldwide, particularly in low- and middle-income countries.

Based on the **most recent updates to the hypertension guidelines**, pharmacists will learn about the essential and optimal standards for measuring blood pressure as well as the risk factors and causes of primary and secondary hypertension.

Pharmacists will also be better informed to counsel patients on the recommended lifestyle modifications for the prevention and management of hypertension.

This module covers both the essential and optimal approaches to the pharmacological treatment of hypertension, the antihypertensive medicines currently available in South Africa and their place in treatment.

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

# The PSSA/Alpha Pharm clinical education programme 2021 for pharmacy staff

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

## Module 5 – Vitamins and minerals

Nutritional supplements have become increasingly popular over recent years. Products designed for children, women, the elderly, athletes and the chronically ill neatly line the shelves in modern pharmacies.

Supplements are products containing vitamins, minerals or other ingredients that are used with the intention of enhancing health, preventing illness and correcting deficiencies. Since the emergence of COVID-19, sales of products marketed for immune health have increased.

To gain a better understanding of supplements and when they should be used, it is necessary to have a basic knowledge of the role of vitamins and minerals in the body. This module explains the functions and role of major vitamins, minerals and trace elements. The recommended daily intakes, as well as the signs and symptoms of nutrient deficiencies (and toxicities) are also explained. Being aware of the use of vitamin and mineral supplements in maintaining health and preventing disease is important for front shop healthcare workers.

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

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Pharmaceutical Society of South Africa

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SCAN ME

**FOR INQUIRIES, EMAIL BRENT SIN HIDGE AT: YPG@PSSA.ORG.ZA**

# To clot, or not to clot – Antithrombotic therapy is the question

**E Osuch,[1] A Marais[2]**

[1] Department of Pharmacology and Therapeutics, School of Medicine, Sefako Makgatho Health Sciences University, South Africa
[2] Department of Pharmacology, School of Medicine, Faculty of Health Sciences, University of Pretoria, South Africa

**Corresponding author, email:** elzbieta.osuch@smu.ac.za

## Abstract

Haemostasis and thrombosis rely on three components, namely the vascular endothelial wall, blood platelets and the coagulation cascade. Non-physiologic excessive thrombosis occurs when haemostatic processes are dysfunctional, causing undue clot formation or reduced clot lysis. Antithrombotic agents including antiplatelet, anticoagulation and fibrinolytic agents are essential for the prophylaxis and pharmacological management of venous thromboembolism and arterial thrombosis. Anticoagulation treatment options have expanded steadily over the past few decades, providing a greater number of agents. Anticoagulants that directly target the enzymatic activity of thrombin and factor Xa have recently been developed to address the inadequacies of traditional vitamin K antagonists. Appropriate use of these agents requires knowledge of their individual characteristics, risks, and benefits.

**Keywords:** anticoagulant, antiplatelet, direct oral anticoagulants (DOACs), haemostasis, thromboembolism, thrombolytic therapy, vitamin K antagonists

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## Introduction

Haemostasis, the process of thrombin-stimulated fibrin clot formation at the site of vessel injury, involves several processes. The clotting process involves endothelial injury and formation of the platelet plug, propagation of the clotting process by the coagulation cascade, termination of clotting by antithrombotic regulatory processes, and clot removal by fibrinolysis.[1] Injury to the endothelium leads to exposure of the circulating blood to subendothelial elements, and activation of platelets and pro-coagulant factors. The main physiologic platelet stimuli include adenosine diphosphate (ADP), thrombin and collagen.[2] Intimal injury impairs the production of nitric oxide and prostacyclin and exposes subendothelial collagen. This results in platelet adherence, platelet activation, and secretion of platelets granules. The integrin glycoproteins GPIa/IIa and GPVI are the two most important platelet collagen receptors, playing critical roles in platelet adhesion and activation. Thrombin activates platelets via G-protein coupled protease-activated receptors (PARs) while ADP binds to two G-protein coupled receptors.[3] Following activation, platelets undergo significant conformational changes via the GPIIb/IIIa receptor on the platelet surface that make the platelets extremely adhesive and leads to binding of both von Willebrand factor (VWF) and fibrinogen. Secretion of platelet granules like ADP, serotonin, and thromboxane A2 ($TXA_2$) stimulate and recruit additional platelets, induce vasoconstriction and have potent mitogenic effects on smooth muscle cells.[4] The interactions between activated platelets and the clotting cascade, exposure of tissue factor at the wound site, and its interaction with factor VIIa generate activated factor X which converts prothrombin to thrombin. Thrombin converts fibrinogen from a soluble plasma protein into an insoluble fibrin clot, activates other pro-coagulant factors including factors V, VIII, XI, XIII, and activates platelets. Thrombin is active in both circulating and clot-bound forms.[5] Components of the intrinsic pathway (i.e., factors VIII, IX, XI) are responsible for amplification of this process.[6] In order to restore vessel patency following haemostasis, the clot must be removed by the proteolytic enzyme, plasmin, which is converted from plasminogen, in the presence of tissue plasminogen activator (tPA). Plasmin activity is regulated by vascular endothelial cells that secrete both protease plasminogen activators, and plasminogen activator inhibitors.[7]

## Antiplatelet drugs

Antiplatelet agents prevent clot formation and growth, and prevent platelet clumping. Antiplatelet drugs are classified according to their site of action. These include drugs that inhibit platelet adhesion, activation, aggregation, and platelet mediated links with inflammation. Platelet activation can be impeded by suppressing the $TXA_2$ pathway, ADP pathway, thrombin and phosphodiesterase (PDE).[8]

**Table I:** Summary of available antiplatelet drugs and mechanism of action

| **Antiplatelet agents** | |
|---|---|
| Thromboxane A2 pathway inhibitors | • aspirin (Ecotrin®, Bayer-Aspirin®, Myoprin®) |
| ADP receptor antagonists | • clopidogrel (Clopiwin 75®, Plavix®)<br>• ticlopidine (Not available in SA)<br>• ticagrelor (Brilinta®)<br>• cangrelor (Not available in SA)<br>• prasugrel (Not available in SA) |
| Phosphodiesterase inhibitors | • dipyridamole (Persantin®) |
| Glycoprotein IIb/IIIa inhibitors | • abciximab (Not available in SA)<br>• epitifibatide (Integrilin®)<br>• tirofiban (Aggrastet®) |

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## Thromboxane A2 (TXA2) pathway inhibitors – aspirin

Aspirin as an antiplatelet agent (in addition to its anti-inflammatory, analgesic and antipyretic effect) at a recommended dose of 75–100 mg daily, is used for the primary and secondary prevention of ischaemic heart disease, stroke and transient ischaemic attack, including the prevention of thrombus formation after cardiac surgery. Aspirin is important in the management of coronary artery disease and acute coronary syndromes. Patients with unstable angina have a 50% risk reduction in the incidence of fatal and non-fatal myocardial infarction if they are on aspirin treatment.[9] Low dose aspirin irreversibly acetylates and inhibits cyclooxgenase-1 (COX-1) (only weakly inhibits COX-2) and the formation of TXA2, thus reducing platelet aggregation. Irreversible binding of aspirin to the COX-1 enzyme ensures the inability of new TXA2 to be synthesised, resulting in a permanent effect lasting throughout the lifespan of the platelet (7–10 days).[10] Gastrointestinal tract irritation, bleeding, hypersensitivity reactions, such as bronchospasm, rhinitis, urticaria, angioedema, and drug interactions are the major side effects associated with aspirin use. Tinnitus, impaired renal function and hepatotoxicity are more likely to be experienced in higher dosages. Elderly patients are more prone to these side effects even in lower dosages. Due to aspirin's mechanism of action and effect on the clotting system, it is contraindicated in patients with peptic ulceration, haemophilia, thrombocytopenia and other bleeding tendencies, including severe renal and hepatic insufficiency. Aspirin use should be avoided in children and adolescents due to the possibility of life threatening Reye's syndrome. It is a highly plasma protein bound agent, and therefore has the potential to displace other drugs (i.e. antidiabetic agents, methotrexate, warfarin) from their binding sites and thus increasing the risk of toxicity. Concomitant use of other thrombolytic agents increases the risk of haemorrhage and gastrointestinal bleeding, and should generally be avoided.[11]

## ADP receptor antagonists – clopidogrel, ticlopidine, ticagrelor, cangrelor, prasugrel

ADP receptor antagonists irreversibly inhibit ADP ($P_2Y_1$ and $P_2Y_{12}$) receptors on platelets. These agents are employed to reduce the risk of fatal myocardial infarction in acute coronary syndrome, with or without ST segment elevation, and for secondary prevention of thromboembolic diseases, stroke and transient ischaemic attack, or in patients with aspirin intolerance.[12] Contraindications include active bleeding, intracranial haemorrhage, and severe liver impairment. Drug interactions with aspirin, heparin, warfarin and NSAIDs increase the risk of gastrointestinal bleeding in particular. Common adverse effects include bleeding, gastrointestinal side effects (bleeding, dyspepsia, abdominal pain and diarrhoea), and CNS effects with dizziness, paraesthesia and headache.[13]

Clopidogrel is activated in the liver and is six times more effective than aspirin in preventing platelet aggregation. It has superior tolerability and fewer incidences of bleeding compared to aspirin and ticlopidine. There is competitive cytochrome P450 2C19 (CYP2C19) inhibition by omeprazole and esomeprazole, therefore pantoprazole should be considered in patients requiring a proton pump inhibitor (PPI) whilst taking clopidogrel.[14] In patients with atrial fibrillation and in those intolerant to warfarin, clopidogrel should be added to aspirin.[12] Ticlodipine displays fewer gastrointestinal effects compared to aspirin. However, reversible neutropenia and thrombotic thrombocytopenic purpura may be experienced in < 1% of patients, necessitating therapeutic drug monitoring and regular blood counts.[15] This drug is no longer available in South Africa.

Ticagrelor and cangrelor are selective and reversible inhibitors of the platelet $P_2Y_{12}$ ADP receptor. Cangrelor is not available in South Africa, but these agents are used in combination with aspirin or clopidogrel to prevent thromboembolic events in patients with acute coronary syndrome. Contraindications for ticagrelor's use include hypersensitivity, active bleeding, inherited bleeding disorders, intracranial haemorrhage, severe liver impairment, and the concomitant use CYP3A4 inhibitors/inducers. It increases plasma levels of statins and digoxin.[16]

Prasugrel is used with aspirin to reduce atherothrombotic events after stenting. It can be co-administered with CYP3A4 inhibitors/inducers, statins and PPIs. Prasugrel causes irreversible inhibition of the platelet $P2Y_{12}$ ADP receptor, which results in a fast, powerful and sustained inhibition of platelet aggregation compared to clopidogrel.[17]

## Phosphodiesterase inhibitors – dipyridamole

Dipyridamole blocks the platelet aggregation response by inhibiting phosphodiesterase activity which is responsible to break down Replace with cyclic adenosine monophosphate (cAMP). In addition, the ability of platelets to establish the re-uptake of adenosine is impaired, thereby resulting in increased plasma concentrations of adenosine. Dipyridamole is used in combination with other antiplatelet drugs for reducing thromboembolic complications associated with prosthetic heart valves, and is used as add-on therapy to warfarin in the secondary prevention of ischaemic stroke and transient ischaemic attack (TIA).[18]

## Glycoprotein IIb/IIIa inhibitors – abciximab, eptifibatide, tirofiban

Glycoprotein IIb/IIIa platelet receptor antagonists block the final pathway in platelet aggregation and clot formation. Tirofiban is the only glycoprotein inhibitor currently available in South Africa. These drugs are expensive and reserved for high-risk patients undergoing percutaneous coronary interventions, as adjunctive to heparin and aspirin for the prevention of ischaemic complications, short term myocardial infarction risk reduction in patients with unstable angina, and ST-segment elevation myocardial infarction (non-STEMI) not responding to conventional therapy.[19] Renal impairment necessitates dose adjustment, and major side effects include bleeding and thrombocytopenia. Overdose is managed by treatment discontinuation, administering desmopressin, platelets and recombinant factor VIIa.[20]

## Fibrinolytic drugs

### *Alteplase (recombinant tissue type plasminogen activator – tPA), streptokinase, tenecteplase, urokinase, lanoteplase and reteplase*

Thrombolytic drugs convert plasminogen to plasmin in order to degrade fibrin and fibrinogen. Therapeutic indications comprise the management of acute thrombotic disorders including acute myocardial infarction (STEMI), ischaemic stroke (if administered within 4 hours from angiographically proven vascular occlusion), acute pulmonary embolism, acute arterial thrombosis and deep vein thrombosis. However, thrombolytic treatment is not recommended for unstable angina and non-Q wave infarction, non-STEMI or superficial thrombophlebitis.[21] Bleeding is the primary complication of thrombolytic therapy and haemorrhagic stroke is the greatest concern. Absolute contraindications to fibrinolytic therapy include previous intracranial haemorrhage, structural cerebral vascular lesions, malignant intracranial neoplasms, ischaemic stroke within three months, suspected aortic dissection, active bleeding or bleeding diathesis, or significant head or facial trauma within three months.[22] Relative contraindications include poorly controlled hypertension (systolic blood pressure > 180 mmHg), ischaemic stroke more than three months previously, dementia or other intracranial pathology, traumatic or prolonged cardiopulmonary resuscitation (> 10 minutes) or major surgery (within < 3 weeks), recent (within two to four weeks) internal bleeding, non-compressible vascular puncture, pregnancy, active peptic ulcer, and current use of anticoagulants. Intraocular haemorrhage from fibrinolytic therapy in patients with diabetes mellitus is rare and diabetic retinopathy should not be considered a contraindication to fibrinolytic therapy in acute myocardial infarction.[23]

Currently available fibrinolytic drugs registered in South Africa include streptokinase (Streptase®), alteplase (Actilyse®) and tenecteplase (Metalyse®). Streptokinase, a polypeptide derived from beta-haemolytic streptococcus cultures, is the most widely used fibrinolytic agent worldwide due to the relatively low cost and reasonable efficacy to safety ratio.[24] It binds to plasminogen, forming an active enzyme that activates plasmin. Streptokinase is less efficacious than alteplase, but displays a lower risk of intracranial haemorrhage. The most common adverse effects include bleeding, allergic reactions and hypotension. Anti-streptokinase antibodies remain elevated for up to 7 years after treatment, suggesting that an allergic reaction may occur with re-treatment many years after the first exposure.[25]

Alteplase (tPA) is a non-antigenic naturally occurring enzyme produced by a number of tissues including endothelial cells. In contrast to streptokinase, it is fibrin-specific, thereby having an increased affinity for plasminogen and enhanced clot lysis. It has a short distribution half-life (about four minutes) and elimination half-life about 35 minutes. Differing from streptokinase, alteplase results in less fibrinogen depletion and is not associated with allergic or hypotensive effects.[26] Oro-lingual angioedema is typically mild and transient. Severe oro-lingual angioedema is rare but may cause partial airway obstruction and require emergency airway management.[27]

Tenecteplase (TNK-tPA) is a genetically engineered, recombinant tissue-type plasminogen activator (tPA) that has a longer plasma half-life allowing for a single intravenous bolus injection. It is approximately 14 times more fibrin specific and has an 80-fold higher resistance to inhibition by plasminogen activator inhibitor 1(PAI-1) than tPA. Tenecteplase bolus administration is less complicated and faster to conduct compared to streptokinase and alteplase.[28]

Urokinase, lanoteplase and reteplase are fibrinolytic agents which are not currently available in South Africa. Reteplase (recombinant plasminogen activator, rPA) is a non-glycosylated deletion mutant of wild-type recombinant tissue-type plasminogen activator (tPA). Reteplase is less fibrin selective and has a longer half-life than alteplase.[29] Urokinase is a nonselective plasminogen activator that has no specific affinity for fibrin, thereby activating fibrin-bound and circulating plasminogen indiscriminately. It is the major activator of fibrinolysis in the extravascular compartment in contrast to tPA which is largely responsible for initiating intravascular fibrinolysis. It is currently used only in the management of pulmonary embolism.[30]

## Anticoagulant drugs

Anticoagulants include a variety of agents that inhibit one or more steps in the coagulation cascade, thereby slowing down clotting, reducing the formation of fibrin or preventing clots from forming. Their mechanisms vary, including direct enzymatic inhibition, indirect inhibition by binding to antithrombin III, and antagonism of vitamin K-dependent factors by altering their hepatic synthesis and calcium-binding properties. Available agents include unfractionated heparin, low molecular weight

**Table II:** Summary of available anticoagulant drugs

| **Anticoagulants** | |
|---|---|
| • Unfractionated heparins | • heparin |
| • Low-molecular-weight heparins (LMWH) | • enoxaparin (Clexane®, Noxfibra®)<br>• dalteparin (Fragmin®)<br>• nadroparin (Fraxiparine®)<br>• fondaparinux (Arixtra®) |
| • Vitamin K antagonists | • warfarin |
| • Non-vitamin K antagonists | |
| ▫ Direct thrombin inhibitors (DTIs) | |
| ▪ Oral direct thrombin inhibitors | • dabigatran (Pradaxa®) |
| ▪ Parenteral direct thrombin inhibitors | • bivalirudin (Not available in SA)<br>• argatroban (Not available in SA)<br>• desirudin (Not available in SA) |
| ▫ Direct factor Xa inhibitors | • rivaroxaban (Xarelto®)<br>• apixaban (Eliquis®)<br>• edoxaban (Not available in SA)<br>• betrixaban (Not available in SA) |

heparins, fondaparinux, vitamin K antagonists, direct thrombin inhibitors, direct factor Xa inhibitors, and other agents at various stages of development.[31]

### *Unfractionated heparins*

Heparin enhances the activity of antithrombin III that in return inhibits the action of factors XII, XI, IX, X and II. Heparin treatment in unstable angina reduces the risk of progression to myocardial infarction and associated mortality by approximately 80%. It is used in the treatment and prophylaxis (especially after abdominal, orthopaedic and gynaecological surgery, or in patients with malignancy) of deep vein thrombosis (DVT), pulmonary embolism (PE), unstable angina, and acute non ST elevated myocardial infarction when rapid anticoagulation is required. Monitoring of partial thromboplastin time is essential.[32] Contraindications for heparin use include hypersensitivity and paradoxical heparin-induced thrombocytopenia associated with thromboembolism. Skin necrosis may occur at the injection site and prolonged use has been associated with osteoporosis. Protamine sulphate is used as a heparin antidote.[33]

### *Low-molecular-weight heparins – enoxaparin, dalteparin, nadroparin, fondaparinux*

Low-molecular-weight heparins (LMWHs) have more anti-Xa activity and longer duration of action compared to unfractionated heparins. These agents display superior anticoagulant predictability, and have a lower incidence of thrombocytopenia. Titrated correctly according to body weight, LMWH provide effective anticoagulation and does not require regular monitoring of the activated partial thromboplastin time. If treatment continues for prolonged periods, regular platelet counts should be performed to monitor for the development of thrombocytopenia. In addition to the same indications as heparin, a combination of LMWH and aspirin should be used instead of unfractionated heparin to treat patients with unstable angina.[34] Fondaparinux is a synthetic pentasaccharide, chemically related to LMWH but with no effect on thrombin (inhibiting only factor Xa) and has a decreased risk of causing bleeding. Although bleeding complications with LMWH are infrequently encountered, there is no antidote available in case of an overdose, and management remains supportive. Fortunately, however, bleeding complications related to LMWH are infrequent.[33]

### *Vitamin K antagonist – warfarin*

Warfarin is an oral anticoagulant effective in primary and secondary prevention of venous thromboembolism and arterial embolism in patients with atrial fibrillation or prosthetic heart valves. It acts by inhibiting the hepatic synthesis of vitamin K dependant coagulation factors II, VII, IX, X, and natural anticoagulant protein C and S.[35] Drug interactions, very slow onset of action (half-life about 40 hours) and inconsistent response are considerable limitations to its use. It has a narrow therapeutic window and more variable dose-response relationship that depends on a variety of factors. These features necessitate the frequent monitoring of clotting times to optimize the therapeutic dose range and prevent bleeding.[36] A wide variety of drug interactions involving multiple mechanisms can occur with warfarin use. These include displacement from the albumin binding sites, inhibition or induction of hepatic cytochrome enzymes, and the interference with absorption and metabolism of other drugs known to have antithrombotic effects. Its effect can additionally be altered by changes in the diet, administration of herbal supplements, the presence of certain gastrointestinal disorders, and acute medical illness. The level of vitamin K intake and production in the gastrointestinal tract, as well as induction of hepatic cytochromes affect warfarin pharmacokinetics. Genetic polymorphisms of the *VKORC1* gene which is responsible of regulating the vitamin K epoxide reductase enzyme, can result in both over- or under coagulation on warfarin treatment, thus dose adjustment may be necessary.[37] Contraindications for its use include bleeding disorders, recent stroke, active or recent bleeding, infective endocarditis, aneurism, severe hypertension, recent eye, brain or spinal cord surgery and hypersensitivity reactions. The risk of bleeding should be carefully evaluated in patients with chronic liver disease, portal hypertension, renal disease and in geriatric and paediatric patients. The international normalised ratio (INR target between 2.5–3.5) should be determined at baseline, then on alternate days for 2 weeks, then weekly for 1 month, thereafter monthly for 1 year and if stable 3 monthly. Patients experiencing difficulty in controlling INR may benefit from direct oral anticoagulants (DOACs). However, vitamin K antagonists remain significantly less expensive than DOACs. Warfarin is highly teratogenic and contraindicated in pregnancy. Low molecular weight heparins are the drug of choice in pregnant females requiring antithrombotic therapy. Warfarin overdose is treated with intravenous administration of vitamin K, followed by factor IX, fresh human plasma, or packed cell concentrate (PCC). Providing recombinant factor VIIa is reserved for patients with life-threatening bleeding complications not responding to conventional therapy.[33]

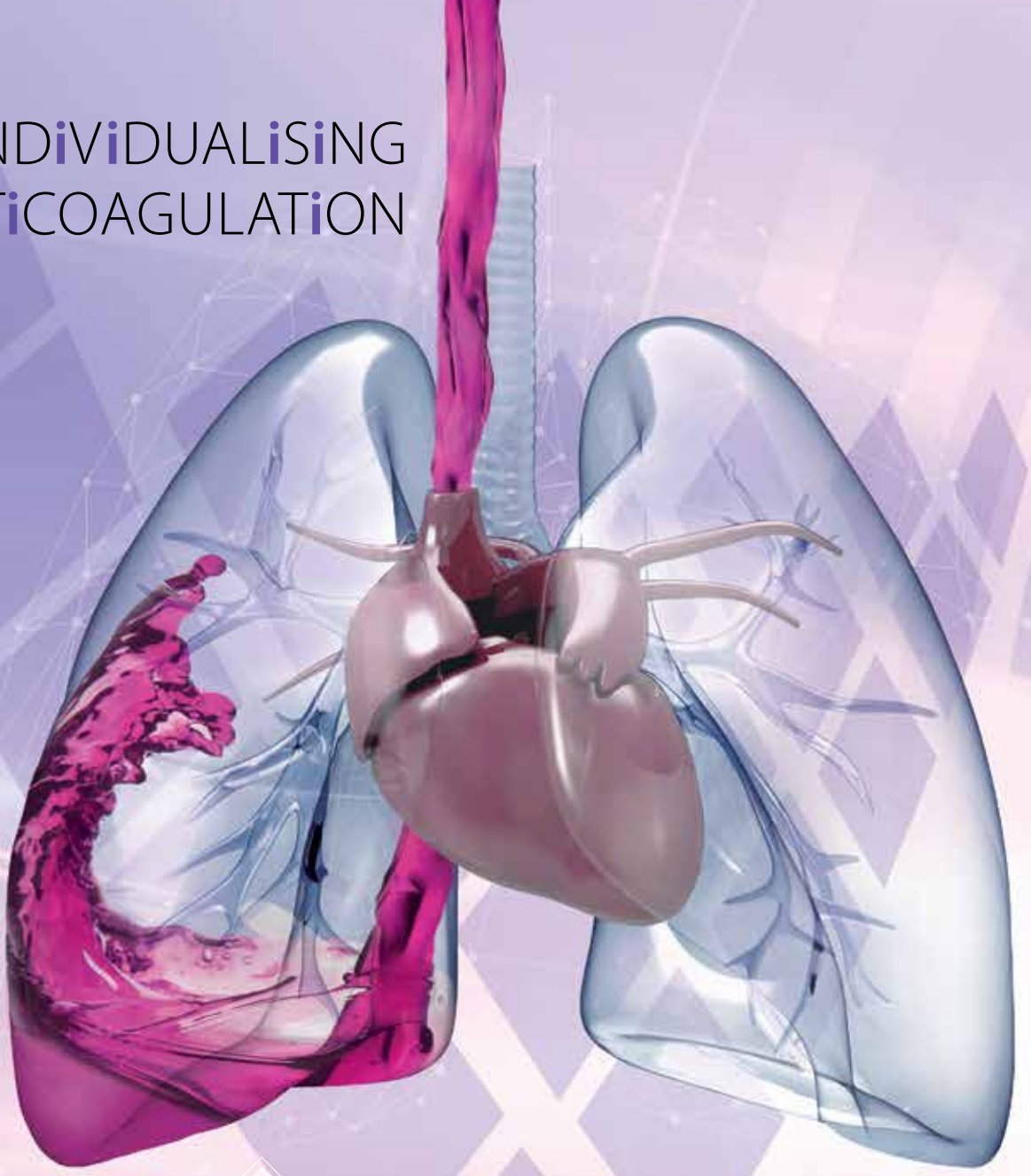
### *Direct oral anticoagulants/novel oral anticoagulants or non-vitamin K antagonists*

The direct oral anticoagulants (DOACs) represent the newer class of non-vitamin K antagonists, only approved as recently as 2010. They differ significantly from vitamin K antagonists in their onset of action, half-life, drug-drug interactions, and availability of antidotes when excessive bleeding may occur. DOACs are administered in the absence of monitoring of drug levels or clotting times. These agents are contraindicated in patients with prosthetic heart valves (due to increased risk of fatal valve thrombosis), pregnancy and severe hepatic impairment. Dose reduction of direct factor Xa inhibitors in patients with renal impairment is recommended.

### *Direct thrombin inhibitors*

Direct thrombin inhibitors (DTIs) prevent thrombin from cleaving fibrinogen to fibrin. They bind to both soluble thrombin and fibrin-bound thrombin. Unlike heparin, the direct thrombin inhibitors do

# iNDiViDUALiSiNG ANTiCOAGULATiON



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**Reference 1.** iXarola Package insert. S4 **IXAROLA® 10, 15, 20** (film-coated tablets). Each film-coated tablet contains 10 mg, 15 mg or 20 mg rivaroxaban. Reg. No.: IXAROLA® 10: 50/8.2/9017, IXAROLA® 15: 50/8.2/9018, IXAROLA® 20: 50/8.2/9019. **NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION (HCR):** Bayer (Pty) Ltd, Reg. No. 1968/11192/07. 27 Wrench Road, Isando 1609. Marketed by Sanofi Aventis South Africa (Pty) Ltd., Reg. No.: 1996/010381/07, 2 Bond Street, Grand Central Ext. 1, Midrand, 1685.
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not require a co-factor such as antithrombin to elicit their effect. In addition, DTIs bind to platelet factor 4 (PF4), and are therefore not able to induce or react with the anti-heparin/PF4 antibodies responsible for causing heparin-induced thrombocytopenia (HIT). Parenteral DTIs are effective anticoagulants for patients with HIT. The oral direct thrombin inhibitors, or oral direct factor Xa inhibitors, are usually administered at fixed doses without laboratory monitoring.[39]

### *Oral direct thrombin inhibitors – dabigatran*

Dabigatran is a prodrug that requires conversion to the active form by the liver. The maximum anticoagulant effect is achieved within 2–3 hours after ingestion. Dabigatran has a half-life of approximately 15 hours, and its absorption is unaffected by food. It is metabolised by the kidney (and not by the cytochrome p450 system), resulting in an extended half-life in elderly patients, or those with renal insufficiency. Dose reduction should be considered in these patients. It is a substrate for P-glycoprotein, therefore concomitant use with P-glycoprotein inducers (e.g., rifampicin) reduces the anticoagulant effect, whereas simultaneous use with P-glycoprotein inhibitors (e.g., ketoconazole, verapamil) may increase the anticoagulant effect.[40] Avoidance of dabigatran in individuals with a body mass index (BMI) > 40 kg/m$^2$, or weight ≥ 120 kg is recommended due to an increased risk of various emboli observed with the fixed dose formulation.[41] Dabigatran is associated with a lower risk of osteoporotic fractures than warfarin.[42] It is indicated in the treatment and prophylaxis of venous thromboembolic disease, stroke circumvention in patients with atrial fibrillation (AF). It should be avoided during pregnancy, or patients with prosthetic heart valves. Laboratory testing prior to initiating dabigatran should include platelet count, prothrombin time (PT), activated partial thromboplastin time (aPTT), and serum creatinine measurement. Routine laboratory monitoring of coagulation times is not required.[43] Premature discontinuation of dabigatran has been associated with an increased risk of intracranial haemorrhage, gastrointestinal bleeding and non-bleeding gastrointestinal events (dyspepsia, gastrointestinal reflux) and other thrombotic events.[44] Idarucizumab (not registered in South Africa) is the only anticoagulant reversal agent for dabigatran.[45]

### *Parenteral direct thrombin inhibitors – bivalirudin, argatroban, desirudin*

None of these agents is currently available in South Africa. They have limited use and are currently only indicated for heparin-induced thrombocytopenia and percutaneous coronary interventions. Bivalirudin is a synthetic amino acid peptide that binds to the thrombin catalytic site reversibly inhibiting thrombin enzymatic activity. Intravenous administration produces an immediate anticoagulant effect. The drug is primarily metabolised by the liver and the kidney. However, patients with renal failure do not require dosage adjustment. The half-life of bivalirudin is approximately 25 minutes and prolonged coagulation times return to normal approximately one hour after discontinuation. Bivalirudin can be haemodialysed and be monitored by the activated clotting time (ACT) and the activated partial thromboplastin time (aPTT), with a target of 1.5 to 2.5 times the normal range.[46] Argatroban is also a synthetic peptide that interrelates with the active site of thrombin. It has a short *in vivo* plasma half-life (terminal elimination half-life approximately 40 to 50 minutes), and is exclusively metabolised by the liver. Argatroban is safe for use in patients with renal dysfunction and no dosage adjustment is required compared to bivalirudin.[47] Desiudin is a recombinant hirudin derivative that inhibits free and clot-bound thrombin. The half-life is approximately two hours and may be increased in patients with renal insufficiency.[48]

### *Direct factor Xa inhibitors – rivaroxaban, apixaban, edoxaban, betrixaban*

Rivaroxaban and apixaban are the only direct factor Xa inhibitors available in South Africa. These agents block the action of both the circulating and clot-bound forms of factor Xa. This mechanism is unlike the indirect factor Xa inhibitors (heparin and fondaparinux) which are only able to inactivate circulating factor Xa via antithrombin.[49] Clinical indications for direct factor Xa inhibitors include venous thromboembolism (VTE) prophylaxis in hip and knee replacement surgery (apixaban & rivaroxaban), VTE treatment – individuals with or without cancer (only Rivaroxaban), stroke and systemic embolism prevention in non-valvular atrial fibrillation (NVAF) (apixaban and rivaroxaban). These drugs have half-lives between 5 and 9 hours, and display drug interactions with dual inhibitors of CYP3A4 and P-glycoprotein such as ketoconazole.[50]

Direct factor Xa inhibitors should be used with caution in patients with creatinine clearance < 30 to 15 ml/min since impaired glomerular filtration will inhibit renal elimination, resulting in an increase in drug exposure. Similarly, drug accumulation could be present in patients with severe hepatic impairment and dose adjustments should be considered in liver diseases. These agents should be avoided during pregnancy. Dabigatran edoxaban or betrixaban should also be avoided in patients with a body mass index (BMI) > 40 kg/m$^2$. Rivaroxaban and apixaban are appropriate anticoagulant options regardless of high BMI.[51] Routine monitoring of coagulation times is not required.[52] A recombinant modified factor Xa protein (andexanet alfa), has recently been approved by the FDA as a reversal agent for rivaroxaban and apixaban in patients with life-threatening, or uncontrolled bleeding.[53] This agent is not yet available in South Africa.

## Conclusion

Although antithrombotic drugs are widely used for the prevention and treatment of arterial and venous thrombosis, thromboembolic diseases are still a major cause of death and disability worldwide. Anticoagulants and antiplatelet drugs are key therapeutic agents in the treatment of cardiovascular diseases. Given different mechanisms of action, combining these agents holds the potential for additive and perhaps even synergistic reductions in thromboembolic morbidity and mortality. Family physicians and

health care professionals have an important role to play in the prevention, treatment and risk reduction of thrombosis, including provision of accurate, up-to-date information to their patients. In addition to pharmacological management, every effort should be made to encourage patients to make healthy lifestyle choices with regards to factors such as smoking, obesity, exercise and their diet.

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***References available on request.***

# Things that can go wrong on holiday

**W Rabbetts**

Amayeza Information Services, South Africa

**Corresponding author, email:** wilna@amayeza-info.co.za

## Abstract

Bites and stings from insects and animals can merely be a nuisance, or they can cause severe local reactions and even life-threatening consequences. Some bites are vectors for serious infections such as malaria, yellow fever, tick bite fever and rabies. Although one should ideally avoid contact with these insects and animals, this is not practical and the approach to how best to minimise the risks and complications of the more common bites and stings, especially over the summer holiday season, will be discussed, as well as a short overview of cuts and bruises, which may also be more likely when travelling away from home.

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## Introduction

Humans are vulnerable to injury from accidents as well as stings and bites from many insects and other animals daily, but even more so when they travel to new places, and as December approaches, more people may be embarking on holidays in exciting places. This article will address some of the bites, stings and other accidents that may occur on holiday and how to prevent or treat them.

## Bites and stings

Is it a bite, or is it a sting, and what is the difference? Although these terms are often used interchangeably, there is a difference. Stings involve the injection of venom via a posterior structure (usually aptly called "a sting"), whereas bites involve structures associated with the mouth. Both result in local reactions, and some may cause severe life-threatening systemic consequences.[1]

### *Bites*

Some of the more common insect bites include bites from ticks, fleas, mosquitoes, spiders and bedbugs. Other than spider bites, they can all be prevented by means of approved insect repellents and/or insecticides. Using insect repellents containing 30% DEET (N,N-diethyl-3-methylbenzamide or N,N-diethyl-m-toluamide) is recommended by the American Academy of Pediatrics (AAP).[2]

#### *Mosquito bites*

Mosquitos may be small and have short lifespans, but they can wreak havoc on human lives. From their itchy bites to the diseases they can carry, mosquitos are often annoying and sometimes downright deadly. There are several different types of mosquitoes, many of which bite humans to obtain a blood meal for their offspring. These tiny insects can transmit some of the deadliest infections. For example, female *Anopheles* mosquitoes, which bite at night (and often don't make any noise), carry malaria, and *Aedes* mosquitoes, which bite during the day, carry yellow fever, dengue and chikungunya. Other mosquitoes may not transmit infections, but they may still cause severe discomfort.

Treatment of these bites consists of mainly over-the-counter antihistamines and topical anti-itch medications. While there is a vaccine against yellow fever and chemoprophylaxis available against malaria, the best form of protection is to not get bitten in the first place, by using an effective insect repellent. Effective repellents include synthetic preparations such as DEET, Picardin (KBR3023), and IR 3535, as well as PMD (P-MENTHANE-3,8-DIOL), which is derived from lemon eucalyptus. For maximal protection against mosquitoes, DEET is preferable over other agents.[3] Examples of DEET containing products in South Africa are Tabard and Peaceful Sleep.

#### *Tick bites*

In South Africa, the most common disease caused by ticks is tick bite fever. There are two distinct types, *Rickettsia conorii,* that tends to be associated with milder disease with little risk of complications and *Rickettsia africae,* that can result in severe or even fatal complications.[4] The incubation period is about five to seven days, after which non-specific symptoms similar to malaria occur. There is an eschar at the site of the bite, but this is not always visible as it may be in areas such as the scalp or behind the ear or between the toes. About three days later, a maculopapular rash appears and often involves the soles and palms.[1,5] Doxycycline is the drug of choice, even for children under the age of eight years. The adult dose is 100 mg twice daily for five to seven days. A clinical response is usually seen within 48 hours. There are increasing published data on the relative safety of doxycycline compared with older tetracyclines in both pregnancies and in children.[6]

Recent studies have shown that DEET applied to exposed skin and permethrin-impregnated clothing is a reasonably effective preventative measure. If the tick is found on the body, it should be carefully removed, using fine-tipped tweezers. The tick should be grasped as close to the skin's surface as possible and pulled upward with steady, even pressure, taking care not to twist or jerk the tick as this can cause the mouthparts to break off and remain in the skin.[4] Do not try to smother a tick with petroleum jelly, nail polish or rubbing alcohol or try to burn the tick while it is stuck to your skin.[7]

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***Spider bites***

Many spider species are found in Southern Africa, but fortunately, not many of them are venomous. The venomous ones are divided into neurotoxic and cytotoxic groups. The neurotoxic group is represented by the widow or button spiders and a bite from one of these will result in a burning pain at the site of the bite, which can spread to the chest, back or abdomen. This is then followed by generalised muscle pain and cramps, especially in the abdomen, chest, back and thighs. Muscle tremors and weakness follows and then also profuse sweating and other neurological symptoms.[8] Medical attention should be urgently sought as administration of antivenom may be required.[1]

The cytotoxic group includes the sac and violin spiders, as well as the six-eyed sand spider. Bites are initially not that painful, but a vesicular or bullous skin lesion may develop and this can progress to local tissue necrosis. There is no antivenom for these bites and antibiotic therapy and surgical debridement are the required treatments.[8] A tetanus toxoid booster is also recommended.[9]

***Bedbugs***

Bed bugs are small, flat insects, reddish-brown in colour, wingless and about 1 to 7 mm in length. Although bed bugs have not been shown to transmit disease, their bites can produce strong allergic reactions and considerable emotional stress.[10] Bed bug bites resemble several other insect bites, but if they are discovered upon wakening, and they form a line or row on the skin, particularly on exposed skin, and are itchy, then one should suspect bed bugs. The bugs and their eggs are seldom seen, as they hide in the crevices during the day. Little brown specks (their dung) on the linen, mattresses and walls surrounding the bed, are telltale signs.[10]

The bites can be treated with an oral antihistamine and/or low-dose topical corticosteroid and the furniture and clothing should be treated appropriately to get rid of the bed bugs. Vacuuming the furniture and washing linen and clothing in hot water and drying them in an electric drier can be effective, but pest control agents may be required.[11]

***Snakebites***

Roughly 11% of the 173 species of snakes in southern Africa can be considered deadly and these include mambas, cobras, the rinkhals, puff adder, gaboon adder, boomslang and the twig snake. The Mozambique spitting cobra accounts for most serious bites, followed by the puff adder, and then the stiletto snake and rhombic night adder. Most of the deaths resulting from snakebite in southern Africa are as a result of Cape cobra and black mamba bites.

In the event of a snakebite, the following symptoms may appear:

- An immediate burning pain, followed by swelling, which progresses up the limb and may affect the lymph glands – the puff adder and the Mozambique spitting cobra (cytotoxic venom).
- Dizziness, difficulty in swallowing and breathing, drooping eyelids and nausea – Cape cobra and mambas (neurotoxic venom).
- Bleeding from the nose, small cuts, followed by bleeding from mucous membranes and, after several hours, severe internal bleeding – the boomslang and the twig snake (haemotoxic venom).
- Shock, which can cause nausea, pain and difficulty breathing.

What you can do

- Get the victim to a hospital as soon as possible.
- Keep the victim calm and as still as possible.
- Remove rings and tight clothing.
- Apply pressure bandage for bites from the Cape cobra and black mamba. The idea is to put pressure on the lymphatic system and, in doing so, reduce the rate at which venom is absorbed.
- Artificial respiration when necessary for snakes with neurotoxic venom.
- In the case of spitting snakes where the venom gets into a victim's eyes, flush the eyes for at least 15–20 minutes with water or any bland liquid like milk if no water is available and then get the victim to a doctor.[12]

It is always advisable to check ahead of visiting an area what snakes are found there and be able to identify and avoid them. For more information, visit https://www.africansnakebiteinstitute.com/snakebite/

***Rabid animal bites***

Human rabies cases are rare in South Africa, but cases are still confirmed annually. Humans are exposed to rabies through bites and other wounds inflicted by rabid animals. The virus is contained in the saliva of a rabid animal. Most human rabies cases in South Africa are associated with domestic dog exposures. In addition to dogs, any bites or scratches from wild animals such as yellow mongoose, black-backed jackal, bat-eared fox, and caracal must all be considered as possible exposure to the rabies virus. Rabies is not typically reported from small rodents such as mice and rats and there are no rabies viruses reported in bats in South Africa.

What should a person do if they have been exposed to a suspected rabid animal?

Wash all wounds and scratches immediately with soap or detergent and flush them thoroughly for about 5–10 minutes with water. Seek immediate medical treatment for post-exposure prophylaxis, which will be given in accordance with the category of exposure.[13] A tetanus shot is also recommended where the patient has not received one in the last five years.

***Stings***

The most common stings that occur are from bees, scorpions and then jellyfish and bluebottles. Apart from the localised pain and

swelling that these stings can produce, some people may also have allergic reactions to the stings and develop anaphylaxis.

***Bee stings***

The most common stings in South Africa are caused by the honeybee. If a bee approaches, one should stand still, and not frighten it. If it lands, one should try gently to blow it off. If a swarm of bees approaches, on the other hand, one should run away as fast as possible, as bees are slow flyers and can normally be outrun. When a bee stings, the barbed sting tears off and stays embedded in the skin, resulting in the death of the bee. The venom that it injects includes enzymes and proteins which give rise to histamine release and an inflammatory reaction. The barbed sting should be carefully removed by scraping the skin as soon as possible, but not by squeezing, as this causes more venom to be injected. Most bee stings cause swelling, pain and redness within minutes, and these can be minimised by applying ice or cold compresses and by taking an antihistamine such as promethazine.

When someone who is allergic to bee venom gets stung, more severe allergic reactions can occur including anaphylaxis. People who are allergic to bee venom should carry a preloaded adrenalin syringe and Medic Alert bracelet or similar warning device.[1]

***Scorpion stings***

There are around 150 scorpion species in southern Africa. There is a great rule of thumb when it comes to scorpions: **The thicker the tail and smaller the pincers, the more venomous it is**. Scorpions are nocturnal and more active during the warmer season. Most stings are accidental when scorpions are stood on or grabbed in the dark, as scorpions would rather escape humans than attack.[14] All the thick-tail venoms require urgent medical treatment with antivenom, and while the stings from the smaller-tailed scorpions are excruciating and the affected area will be very sensitive to touch, these stings are not serious.[15]

***Jellyfish and bluebottles***

At the coast, jellyfish and bluebottle stings occur frequently. If someone is stung by either of these, a welt or rash develops. Rinse the sting site with seawater and remove the tendrils carefully. For patients with significant pain, treatment with hot water immersion or application of hot packs rather than cold therapy or irrigation with vinegar is recommended. Take care, however, not to scald the skin.[16] Stings from sea urchins or starfish can be rapidly inactivated by applying heat, as they are heat-labile venoms.[1]

## *Cuts and bruises*

Slips, trips and falls happen easily when on holiday, so knowing how to treat cuts and bruises is important. Bruises will mostly heal on their own, but the following measures help:

- apply a cold pack for 15 minutes every 1–2 hours,
- raise the area,
- take medication to reduce pain and swelling, and
- do **not** use a warm pack or heating pad on the bruise.[17]

For cuts that do not go all the way through the skin, no stitches will be necessary. Treatment of most cuts start by cleaning the area with soap and water and removing any debris that may be present. If the cut is bleeding, press a clean cloth or bandage firmly to the area for 20 minutes and elevate it above the level of the heart. A thin layer of antibiotic ointment, for example an ointment containing mupirocin, and a clean bandage, is all that is needed for cuts that do not need stitches.[17] A tetanus booster could also be indicated if the patient has not had one in the last 5–10 years, especially if the cut is dirty or deep.

Travelling can increase risks to personal health and well-being, and these risks should be understood when planning travel, particularly to unfamiliar, distant or remote areas. Taking appropriate precautions before beginning a trip can reduce these risks and ensure a plan is in place in the event of injury. The pharmacist can play an important role in helping people pack the necessary first-aid products by checking where the customer is going and advising on what they might need when they get to their holiday destination.

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# The pharmacological management of depression

**E Osuch,[1] A Marais[2]**

[1]Department of Pharmacology & Therapeutics, School of Medicine, Sefako Makgatho Health Sciences University, South Africa

[2]Department of Pharmacology, School of Medicine, Faculty of Health Sciences, University of Pretoria, South Africa

**Corresponding author, email:** elzbieta.osuch@smu.ac.za

## Abstract

Depression affects nearly 350 million people worldwide. Local data indicates that approximately 17% of all South Africans will experience at least one episode of depression in their lifetime. Depressive disorders contribute significantly towards overall morbidity and increased risk for suicide. Antidepressant therapy remains one of the cornerstones in the management of depressive disorders. Although the efficacy of antidepressive drugs is continuously subjected to criticism, thousands of controlled clinical trials have shown, and will continue to show, their benefit in the effective treatment of depressive disorders. Since the introduction of antidepressants in the early 1950s, researchers have been searching for an ideal antidepressant able to adequately reduce, preserve and prevent features of depression with the absence of side effects. This article summarises the currently available antidepressant drugs in South Africa. Discontinued products have been omitted and newly registered agents have been added. This review does not contain reference to any experimental drug, or substances not yet available for local use.

**Keywords:** major depressive disorder, antidepressant, serotonin, noradrenaline, dopamine

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## Introduction

It is estimated that 350 million people worldwide suffer from depression and predictions indicate that by the year 2020 major depressive disorder (MDD) will be the second-largest contributor to the global burden of disease, only being surpassed by heart disease.[1] Depression affects approximately one in 15 adults (6.7%), whereas one in six individuals (16.6%) will experience at least one lifetime episode.[2] More than 800 000 people commit suicide each year, and it is estimated that about 50% of depressed patients have a history of at least one suicide attempt during their lifetime. Suicide is the second leading cause of death in the age group 15–29 years.[3] Limited data regarding the epidemiology of MDD in South Africa is available, however, studies conducted from 2008 to 2012 showed a 41% increase in the incidence of mental disorders. Of these disorders, MDD was shown to have a 12-month prevalence of 16.5% and a lifetime prevalence of 30.3%.[4] Research done by the Faculty of Mental Health at the University of Cape Town shows that nearly three-quarters of South Africans diagnosed with mental illness are not receiving treatment and that 11% of all non-natural deaths in South Africa are the result of suicide.[5]

## Clinical characteristics of depressive disorders

MDD is usually associated with severe and persistent symptoms leading to impairment in psychosocial functioning and increased mortality. Symptoms of depression may include fatigue, anhedonia, restlessness, subjectively depressed mood, psychomotor retardation, cognitive impairment, weight and appetite changes, sleep disturbances, feelings of guilt and worthlessness and thoughts of death or suicide. Depressive symptoms must be present for a period of at least two weeks in order to make a clinical diagnosis.[6] Depressive episodes differ in the number and severity of symptoms and are categorised as mild, moderate, or severe. MDD is typically a recurrent disorder with an estimated relapse rate of approximately 50–85%.[7] The history of manic episodes being present or absent in a depressed patient is important since different treatment approaches need to be considered. Bipolar affective disorder consists of manic and depressive episodes which are intermittently separated by periods of normal mood. Manic episodes are characterised by the presence of elevated or irritable mood, over-activity, inflated self-esteem and a decreased need for sleep. Both MDD and bipolar disorder may become chronic if untreated.[8]

## Pathophysiology of depression

Depression is clinically and etiologically a heterogenic disease, although the exact pathophysiology still remains largely elusive. Theories have suggested that the disorder may be the result of a complex interaction between social, psychological and biological factors. These include genetic factors, psychosocial stress and stress hormones, neurotransmitter imbalance, and changes in the circadian rhythm. Different theories regarding the pathophysiological cause, including the considerable variation in symptoms and disease progression in individual patients presenting with the disorder, have resulted in the

absence of a singular unified hypothesis for depression.[9] As a result, antidepressant treatment, including psychological and biological approaches should be individualised for each patient. Notwithstanding this approach, the high rate of treatment failure remains a serious concern.[10]

Genetic factors are responsible for 30–40% of patients susceptible to MDD.[11] Literature provides consistent evidence on the relation in volume loss of the hippocampus and other brain regions, and the duration of depressive symptoms.[12] Glucocorticoid neurotoxicity, glutamatergic toxicity, decreased neurotrophic factors, and decreased neurogenesis have additionally been proposed as possible mechanisms explaining brain volume loss in depressed patients.[13,14] This suggests that untreated depressive disorders result in hippocampal volume loss, increased stress sensitivity and an upsurge in the risk of recurrence.[15]

Altered stress hormone secretion is more prominent in depressed individuals with a history of childhood trauma.[16] In addition, the physiological response to stress has been shown to be partly gender-specific. Females have a superior stress responsiveness compared to their male counterparts, which is consistent with the higher incidence of MDD in women.[14,17] Hypercortisolaemia with elevated cerebrospinal fluid levels of corticotropin-releasing hormone (CRH) have furthermore been found present in patients with severe and psychotic depression.[18] Cytokines such as interleukin-1α, tumour necrosis factor-α, and interleukin-6, emanating via the release of glucocorticoids, activate the hypothalamic-pituitary adrenal (HPA) axis.[19] HPA axis activation in turn, causes an inflammatory response which may lead to impairment of the central serotonin system, thereby resulting in symptoms of depression.[20] Despite this well documented association, pharmacological modulation of the HPA axis as antidepressant therapy has been dismal.

Monoamine-deficiency and depletion of central nervous system (CNS) neurotransmitters (serotonin, noradrenaline and dopamine) has proved to be the most clinically relevant neurobiological theory in the pathophysiology of depression. Drugs which inhibit monoamine reuptake, thereby causing an elevated concentration in the synaptic cleft, are well known for their clinical effectiveness as antidepressant therapy.[21] Abnormalities in relative serotonin levels, and especially the serotonin-1A (5HT-1A) receptor responsible for regulating serotonin function, has been implicated as a major cause of depression. Decreased expression of this receptor has been found in multiple brain areas of patients with MDD.[22] An increased presence of the central monoamine oxidase enzymes (MAO) responsible for the breakdown of serotonin will cause serotonin deficiency, thereby culminating in depression.[23] In addition, loss-of-function mutations in the gene coding for the brain-specific enzyme tryptophan hydroxylase-2 may explain the loss of serotonin production as a rare risk factor for depression.[24] Dysfunction of the central noradrenergic and dopaminergic systems is furthermore responsible for the pathophysiology in MDD. Here, a reduction in the total concentration of gamma-aminobutyric acid (GABA) in the prefrontal and occipital cortex, together with a debilitated glutamate neurotransmitter system may cause depressive symptoms. In addition, episodes of chronic stress reduce GABA-A receptor function, possibly through changes in neuroactive steroid synthesis.[25,26]

## Treatment goals

All other medical conditions responsible for depressive symptoms have to be excluded before a diagnosis of depressive disorder should be made. A wide range of effective multidisciplinary treatment is available for MDD. These include pharmacotherapy and psychotherapy (e.g. cognitive-behavioural therapy, interpersonal therapy). The choice of treatment should be individualised and based on a meticulous diagnostic assessment of symptoms (physical examination and laboratory investigations), comorbid psychiatric conditions (mental status, psychoactive substance abuse and suicide risk), general medical conditions (thyroid disease, cardiovascular disease, dementia, stroke, and metabolic syndrome), treatment history, social history, occupational history and family history.

Each phase in the successful treatment of depression has a different aim and requires a favourable "response", which is generally measured by a 50% reduction in the patient's depression score.[27] Ultimately the aim is to achieve full remission and the elimination of depressive symptoms with depression scores within the normal range.

- Acute phase – treatment should induce remission of all symptoms.
- Continuation phase – treatment should preserve remission.
- Maintenance phase – treatment should prevent the recurrence of subsequent major depressive episodes.

## Pharmacological options

In addition to psychotherapeutic treatment, various pharmacological agents are available in the management of depression. Some of the newer drugs have not achieved South African registration yet, and are therefore not included in this summary. The currently available drugs are listed in Table I. These include selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), serotonin-noradrenaline reuptake inhibitors (SNRIs), and atypical antidepressants. Atypical antidepressants are further classified as dopamine reuptake inhibitors (DRIs), tetracyclic antidepressants, serotonin receptor antagonists and reuptake inhibitors (SARIs), selective noradrenaline reuptake inhibitors (NTIs), multimodal antidepressants, melatonergic agonists, and various herbal and complementary medicines (e.g. St John's wort). As a rule, monotherapy with benzodiazepines are not recommended, and are only indicated as short-term adjunctive therapy in the initial symptomatic management of anxiety, insomnia, and agitation. Benzodiazepines should be avoided in depressed patients with comorbid substance-abuse disorders.[28]

The choice of drug should primarily be guided by the safety and tolerability profile, contraindications, history and response to

previous treatment, and patient compliance. Cost and product availability should be considered and may contribute to treatment failure. Other factors responsible for treatment failure include medication non-compliance, inadequate duration of therapy, inadequate dosing and misdiagnosis. For a clinical response to become evident, it is necessary to continue treatment for 2–12 weeks at a therapeutic dose. Treatment for MDD should be altered if the patient does not have an adequate pharmacotherapeutic response within 6–8 weeks. Patients presenting with a first episode of MDD in the absence of suicidal risk require treatment for at least 4–9 months after a satisfactory response has been achieved. In patients with a history of two or more depressive episodes, a longer course of maintenance treatment may prove beneficial.[29]

### *Selective serotonin reuptake inhibitors*

SSRIs are some of the most widely prescribed groups of drugs worldwide. At the time of writing this report, 55 individual generic and originator SSRI products were available for prescription by South African doctors. These include citalopram, escitalopram, fluoxetine, paroxetine, fluvoxamine and sertraline. All SSRIs share a similar mechanism of action and general receptor-mediated side effect profile. Individual compounds, however, differ in their pharmacokinetic and pharmacodynamic properties, resulting in varying efficacies. The pharmacological effect is achieved by selectively blocking serotonin reuptake at the presynaptic neurons, thereby increasing the concentration of serotonin in the synaptic cleft. Pure SSRIs have negligible selectivity for other monoamine transporters, thus thwarting side effects associated with activity at muscarinic, α- adrenergic and histaminic receptors. Common adverse effects include gastrointestinal upset (nausea, decreased appetite, diarrhoea, and dry mouth), CNS effects (insomnia, sedation, dizziness, and headache), sexual dysfunction, weight gain, anhedonia and fatigue.[30]

SSRIs are metabolised by the liver cytochrome P450 enzyme system and may therefore inhibit the metabolism of various other drugs making use of this pathway – resulting in toxic plasma concentrations of those substances. In addition, the combination of SSRIs with other serotonergic agents may result in serotonin syndrome, which is marked by agitation, confusion, sweating, pupil dilatation and hyperthermia. Complications include seizures and muscle rhabdomyolysis. Most SSRIs display a high rate of plasma protein binding, which can lead to increased therapeutic or toxic effects of other protein-bound medications. Except for citalopram, SSRIs are unproblematic in patients with cardiac disease. These side effects are less prominent compared to other antidepressive agents, therefore ensuring treatment preference. Based on the convenient dosing profile and low incidence of toxicity, SSRIs are the first line of treatment for acute MDD, including late-onset depression.[31] All SSRIs have an increased risk of suicide, especially in children and adolescents. Administering an SSRI, however, remains the first-line treatment. The suicidal risk should be balanced against clinical benefits and close monitoring should be in place.[28]

Citalopram and escitalopram appears to be the best tolerated, followed by fluoxetine, sertraline, paroxetine and fluvoxamine.

### *Tricyclic antidepressants*

TCAs currently available in South Africa include amitriptyline, imipramine, clomipramine, dothiepin and trimipramine. TCAs have a longstanding record in the effective management of depressive disorders with anxiety or somatic manifestations. These agents principally block noradrenaline and serotonin reuptake. In addition they also block serotonergic, histaminic, α-adrenergic and muscarinic receptors. Recently their usefulness has declined as a result of the unfavourable side-effect profile and considerable toxicity in overdose. The adverse effects of TCAs are related to its anticholinergic and antihistaminic properties. Common side effects include sedation, dizziness, hypotension, blurred vision, confusion, dry mouth, constipation, urinary retention, sexual dysfunction and weight gain. Caution should be taken when treating patients with cardiac conduction abnormalities, since tricyclic antidepressants may prolong the QT interval, thereby causing ventricular dysrhythmia and increase mortality. TCAs have a narrow therapeutic index, where a dose of approximately six times the upper limit may prove fatal. The use of these agents is therefore reserved as an alternative for depressed patients not responding to first-line treatment with an SSRI.[32] TCAs are substrates for the CYP2D6 and CYP1A2 hepatic isoenzymes, and their effect may therefore be potentiated by other inhibitors or substrates requiring these cytochromes (e.g. quinidine, cimetidine, SSRIs, and ritonavir) for metabolism. Combination use with other serotonergic agents will result in serotonin syndrome as described above.

### *Monoamine oxidase inhibitors*

MAOIs include moclobemide (reversible), and tranylcypromine (irreversible). MAOIs inhibit the monoamine oxidase enzyme responsible for the breakdown of catecholamines in the synaptic cleft. Inactivation of the monoamine oxidase enzymes therefore increases the available concentration of noradrenaline, serotonin and dopamine. These agents are accomplished in treating a wide range of depressive disorders especially associated with atypical features such as hypersomnia, increased appetite and weight gain. Patients being treated with MAOIs should avoid food containing tyramine due to the risk of developing a hypertensive crisis. MAOIs should not be administered less than five weeks after the discontinuation of fluoxetine or less than two weeks for other SSRIs in order to prevent the occurrence of serotonin syndrome. Similarly, SSRIs should not be prescribed within two weeks after suspending MAOI treatment.[33]

### *Serotonin-noradrenaline reuptake inhibitors*

Venlafaxine, desvenlafaxine and duloxetine can be used as first-line agents in the treatment of depression. These drugs are vigorous selective inhibitors of the presynaptic reuptake of serotonin and noradrenaline, thereby allowing treatment of a wider range of symptoms. SNRIs have no effect on histaminic,

α-adrenergic or dopaminergic receptors. They are useful in patients with additional anxiety disorders (OCD, ADHD), significant fatigue (menopausal symptoms) or pain syndromes (neuropathic pain, fibromyalgia) associated with depression.[34] SNRIs are used as second-line treatment in individuals not responding to SSRIs. The concurrent use of SNRIs with other antidepressants or patients with major eating disorders is not recommended.[35] The safety, tolerability, and side-effect profiles of SNRIs are similar to SSRIs, however, treatment initiation requires a low dose which should be gradually increased until symptom improvement is noticed. Abrupt withdrawal causing the "discontinuation syndrome" is more pronounced with SNRIs compared to SSRIs.

### *Dopamine reuptake inhibitors*

The use of selective DRIs in depression is limited due to their high abuse potential resulting from an increased dopamine concentration and dopaminergic neurotransmission in the brain. Bupropion is currently the only DRI registered for the management of MDD in South Africa. It is preferable over SSRIs because of a decreased likelihood in causing sexual dysfunction, weight gain and gastrointestinal side effects.[36] Adverse effects include dry mouth, vision disturbances, changes in appetite, tinnitus, confusion and seizures. Sustained-release preparations are more tolerable. Bupropion is contraindicated in patients with epileptic disorders.

### *Tetracyclic antidepressants*

Tetracyclic antidepressants are closely related to the tricyclic antidepressants, only differing in their chemical ring structure. They are multi-potent receptor blockers and act by increasing central noradrenergic and serotonergic neurotransmission. The pharmacological effect is achieved by blocking 5-HT1, 5-HT2, 5-HT3, alpha2-, and histamine (H1) receptors. Sedation and weight gain are the main adverse effects but tend to improve over time. Severe cardiotoxicity has led to most of these agents being withdrawn from the market. The use of tetracyclic antidepressants has largely been replaced by newer agents with fewer side effects.

### *Serotonin receptor antagonists and reuptake inhibitors*

Trazodone acts predominantly as a 5-HT2A receptor antagonist and therefore has similar properties to the SSRIs. In addition, it is an antagonist of H1 and alpha1 adrenergic receptors. Lower doses of trazodone required to be an effective antidepressant are needed to cause sedation and is therefore rather used in the management of insomnia than for its antidepressant effects.[37]

### *Selective noradrenaline reuptake inhibitors*

Reboxetine selectively inhibits noradrenaline reuptake into the presynaptic neurons. It is a low-risk antidepressant compared to the DRIs and is useful in depressed patients with marked apathy, cognitive slowing or psychomotor retardation. Side effects include insomnia, sweating, tachycardia, weight loss, dry mouth and changes in blood pressure.[38]

### *Multimodal antidepressants*

Vortioxetine is the latest agent used in the management of MDD. It is classified as a serotonin modulator and stimulator. Although the mechanism of action is not yet fully understood, it enhances serotonergic activity in the CNS through the inhibition of reuptake of serotonin by 5-HT3 antagonist and 5-HT1A agonist. It displays a more favourable side effect profile, less weight gain, less sexual dysfunction and superior compliance compared to SSRIs, SNRIs and agomelatine. Vortioxetine is safe for use in the elderly. The most common adverse effects include nausea, headache and diarrhoea.[39]

### *Melatonergic agonists*

Agomelatine has a unique mechanism of action, not shared by any of the known antidepressants. It has no effect on monoamine uptake, and has no affinity for adrenergic, histaminergic, cholinergic or dopaminergic receptors. Agomelatine is an agonist on MT1 and MT2 receptors, and an antagonist on 5-HT2C receptors in the frontal cortex. It therefore increases noradrenaline and dopamine release directly and resynchronises circadian rhythms. Additional indications include treatment of anxiety disorders, bipolar depression and obsessive-compulsive disorder. Side effects are rare and include sweating, gastrointestinal disturbances, headache, anxiety, dizziness and raised liver enzymes. A few case reports have indicated 0.1% of patients experiencing mania, suicidal ideation, hallucinations and liver failure.[40] It is contraindicated in liver and kidney impairment and acts as a substrate of CYP1A2, CYP2C9 and CYP2C19. Agomelatine should not be used in children under 18 years since there is still a lack of safety data.

### *Herbal remedies*

St John's wort (*Hypericum perforatum*) is a herbal remedy available over the counter. The exact mechanism of action is not known, but studies suggest it may act as an SSRI. It is only used in the management of mild to moderate depressive symptoms and is not recommended as a first-line treatment modality. St John's wort lacks the adverse effects on sexual function and is not associated with any anticholinergic side effects.[41] Potentially serious drug interactions with protease inhibitors, NNRTIs and cycloserine have been described as a result of CYP3A4 enzyme induction.[42]

### *Treatment-resistant depression*

Up to two-thirds of depressed patients fail to respond on first-line therapy. Presently, no variables have been identified to reliably predict if an individual will respond or not.[43] Patients presenting with treatment-resistant depression should be assessed on the accuracy of diagnosis, presence of comorbid conditions (e.g. substance abuse, anxiety disorders, personality disorders), adequacy of medication dose, duration of treatment, and adherence to the treatment regimen. Possible interventions may include increasing the dose to the maximum tolerated amount, augmenting the current medication with another antidepressant,

**Table I:** Available agents in the management of depression in South Africa

| Active ingredient | Trade name | Strength | Dosage | Comments |
|---|---|---|---|---|
| **Selective serotonin reuptake inhibitors (SSRIs)** | | | | |
| **Citalopram** | Arrow Citalopram® | 20 mg<br>40 mg | Start at 20 mg and increase by 20 mg/d for 1–2 weeks until desired response is reached.<br>Max 40 mg/d. | Additional indication in obsessive-compulsive disorder and panic disorder.<br>Off-label use for generalised anxiety disorder and premenstrual dysphoric disorder.<br>Second-line alternative in paediatric patients not responsive to fluoxetine or sertraline.<br>Least likely SSRI to cause weight gain.<br>Least likely SSRI associated with erectile impairment, but may cause anorgasmia.<br>May cause QT prolongation at doses ≥ 40 mg.<br>Second least likely SSRI to cause drug interactions (inhibits CYP1A2+, CYP2D6+). |
| | Austell Citalopram® | 10 mg<br>20 mg<br>40 mg | | |
| | Bio Citalopram® | 20 mg | | |
| | Cilate® | 20 mg | | |
| | Cilift® | 20 mg | | |
| | Ciloram® | 20 mg | | |
| | Cipramil® | 20 mg | | |
| | Depramil® | 20 mg<br>40 mg | | |
| | Recita® | 20 mg | | |
| | Talomil® | 20 mg | | |
| **Escitalopram** | Accord Escitalopram® | 10 mg<br>20 mg | Start at 10 mg/d and increase to 20 mg/d. | Additional indication in obsessive-compulsive disorder, panic disorder, social anxiety disorder, generalised anxiety disorder.<br>Off-label use for premenstrual dysphoric disorder, fibromyalgia, posttraumatic stress disorder, Raynaud phenomenon.<br>Not licensed in South Africa for the use in paediatric patients.<br>Least likely SSRI to cause drug interactions (inhibits CYP2D6+). |
| | Aspen Escitalopram® | 10 mg | | |
| | Cipralex® | 10 mg<br>20 mg | | |
| | Citraz® | 10 mg<br>20 mg | | |
| | Dolin® | 10 mg<br>20 mg | | |
| | Escitalopram Winthrop® | 5 mg<br>10 mg<br>20 mg | | |
| | Lexamil® | 5 mg<br>10 mg<br>20 mg | | |
| | Marprem® | 5 mg<br>10 mg<br>20 mg | | |
| | Mylan Escitalopram® | 10 mg<br>20 mg | | |
| | Zitolex® | 10 mg<br>20 mg | | |
| | Zytomil® | 10 mg<br>20 mg | | |
| **Fluoxetine** | Deprozan® | 20 mg | Start at 10 mg/d and increase to 20 mg/d if necessary.<br>Max 60 mg/d. | Additional indication in bulimia nervosa.<br>Off-label use for obsessive-compulsive disorder, panic disorder, social anxiety disorder, generalised anxiety disorder, impulse control disorder, personality disorders.<br>First-line treatment in paediatric and adolescent patients.<br>May cause initial weight loss (1st month), thereafter weight gain.<br>Increase awakenings and reduce REM sleep.<br>Second most likely SSRI to cause drug interactions (inhibits CYP1A2+, CYP2C9++, CYP2C19++, CYP2D6+++, YP3A4+, CYP2B6+). |
| | Fluoxetine Actor 20® | 20 mg | | |
| | Lilly-Fluoxetine® | 20 mg | | |
| | Lorien® Tab<br>Lorien® Cap | 20 mg | | |
| | Nuzak® | 20 mg | | |
| | ProHexal® C | 20 mg | | |
| | Prohexal® T | 20 mg | | |
| | Prohexal® T | 40 mg | | |
| | Prozac® C | 20 mg | | |
| | Prozac® T | 20 mg | | |
| | Ranflocs® | 20 mg | | |
| | Sandoz-Fluoxetine® | 20 mg | | |

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| **Fluvoxamine** | Luvox® | 100 mg | Start at 50 mg/d, may increase to 150 mg/d after a week if tolerated. | Additional indication for obsessive-compulsive disorder.<br>Off-label use in anxiety disorder, posttraumatic stress disorder, pain disorder.<br>Not licensed in South Africa for paediatric use.<br>High incidence of withdrawal symptoms.<br>Highest incidence of GI side effects.<br>First most likely SSRI to cause drug interactions (inhibits CYP1A2+++, CYP2C9++, CYP2C19+++, CYP2D6+, CYP3A4+, CYP2B6+). |
| | Faverin® | 100 mg | | |
| **Paroxetine** | Adco-Paroxetine® | 20 mg | Start at 20 mg/d and increase by 10 mg increments according to response.<br>Max 50 mg/d. | Additional indication in obsessive-compulsive disorder, panic disorder, social anxiety disorder, generalised anxiety disorder.<br>Third most likely SSRI to cause drug interactions (inhibits CYP1A2+, CYP2C9+, CYP2C19+, CYP2D6+++, CYP3A4+, CYP2B6+++).<br>Increase awakenings and reduce REM sleep.<br>Most likely to cause sexual dysfunction in males and females.<br>Higher incidence of withdrawal symptoms due to short half-life.<br>Contraindicated in pregnancy.<br>Avoid in paediatric use. |
| | Aropax® | 12.5 mg CR<br>20 mg<br>25 mg | | |
| | Deparoc® | 20 mg | | |
| | Lenio® | 20 mg | | |
| | Paxil® | 20 mg | | |
| | Paroxetine Unicorn® | 20 mg | | |
| | Serapress® | 20 mg | | |
| | Texine® | 20 mg | | |
| | XET 20® | 20 mg | | |
| **Sertraline** | Aspen Sertraline® | 50 mg<br>100 mg | Start at 50 mg/d, may increase to 200 mg/d after a week if tolerated. | Additional indication in obsessive-compulsive disorder, panic disorder.<br>Off-label use in social anxiety disorder, generalised anxiety disorder, posttraumatic stress disorder.<br>Reduces nocturnal wakefulness.<br>Highest incidence of insomnia.<br>Fourth most likely SSRI to cause drug interactions (inhibits CYP1A2+, CYP2C9+, CYP2C19+, CYP2D6+, CYP3A4+, CYP2B6+).<br>Alternative to fluoxetine in paediatric use. |
| | Austell Sertraline® | 50 mg<br>100 mg | | |
| | Dyna Sertraline® | 50 mg<br>100 mg | | |
| | Serdep® | 50 mg<br>100 mg | | |
| | Serlife® | 50 mg<br>100 mg | | |
| | Sertra® | 50 mg | | |
| | Sertraline Winthrop® | 50 mg | | |
| | Zolid® | 50 mg<br>100 mg | | |
| | Zoloft® | 50 mg | | |
| **Tricyclic antidepressants (TCAs)** | | | | |
| **Amitriptyline** | Trepiline® | 10 mg<br>25 mg | Initial dose of 25 mg at bedtime.<br>Increase in 25 mg increments every 3–7 days to 150 mg/day. | Additional indication in anxiety disorders and nocturnal enuresis in children over 11 years of age.<br>Used off-label for chronic pain management, diabetic neuropathy, migraine prophylaxis, and post-traumatic stress disorder.<br>Due to sedating effect useful in patients with insomnia.<br>ECG monitoring is recommended. |
| | Sandoz Amitriptyline® | 25 mg | | |
| **Imipramine** | Tofranil® | 10 mg<br>25 mg | Initial dose of 10 mg.<br>Increase in 25 mg increments every 3–7 days to max 100 mg/day. | Additional indication in anxiety disorders, nocturnal enuresis in paediatric patients over five years of age. |
| | Ethipramine® | 10 mg<br>25 mg | | |

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| **Clomipramine** | Anafranil®<br>Clomidep®<br>Equinorm® | 10 mg<br>25 mg<br>SR 75 mg<br>10 mg<br>10 mg<br>25 mg | Initial dose of 25–50 mg.<br>Increase in 25 mg increments, max 150 mg/day. | Additional indication in cataplexy, narcolepsy, obsessive-compulsive disorder.<br>Off-label use for peripheral neuropathy, ADHD, premature ejaculation.<br>Consider use in paediatric patients not responding to SSRIs or when contraindicated. |
| **Dothiepin** | Thaden® | 25 mg<br>75 mg | Initial dose of 25–50 mg. Increase in 25 mg increments, max 150 mg/day. | Additional indication in anxiety disorders. |
| **Trimipramine** | Tydamine® | 25 mg<br>50 mg | Initial dose of 25–50 mg. Increase in 25 mg increments, max 300 mg/day. | Pronounced anticholinergic effects and most sedating TCA. |
| **Monoamine oxidase inhibitors (MAOs)** | | | | |
| **Moclobemide** | Depnil® | 150 mg<br>300 mg | Initial dose of 300 mg/day. Max 600 mg/day. | Avoid with serotonergic drugs.<br>Wash out period of at least two weeks when used with SSRIs. |
| **Tranylcypromine** | Parnate® | 10 mg | Initial dose of 10 mg.<br>Increase to max 30 mg after two weeks | Avoid with food containing tyramine due to possibility of hypertensive crisis (cheese, pickled herring, yeast, meat extract and fermented meat, red wine, yoghurt, caviar, avocados, figs).<br>Contraindicated in severe hepatic and renal dysfunction, pheochromocytoma, and alcoholism. |
| **Serotonin-noradrenaline reuptake inhibitors (SNRIs)** | | | | |
| **Venlafaxine** | Efegen XR® | 75 mg<br>150 mg | Initial dose of 37.5 mg daily for a week.<br>If tolerated, increase to 75 mg daily for a week. Increase no more than 75 mg every four days.<br>Max 375 mg/day. | Use with caution in cardiac disease.<br>Less sexual dysfunction than SSRIs.<br>Third-line use in paediatric patients not responding to first- or second-line SSRI.<br>Highest incidence of discontinuation syndrome. |
| | Efexor XR® | 75 mg<br>150 mg | | |
| | Illovex SR® | 37.5 mg<br>75 mg<br>150 mg | | |
| | Odiven® | 37.5 mg<br>75 mg | | |
| | Sandoz-Venlafaxine® | 75 mg<br>150 mg | | |
| | Venlafaxine Unicorn XR® | 75 mg<br>150 mg | | |
| | Venlafaxine XR Adco® | 37.5 mg<br>75 mg<br>150 mg | | |
| | Venlor XR® | 37.5 mg<br>75 mg<br>150 mg | | |
| **Desvenlafaxine** | Exsira® | 50 mg<br>100 mg | Initial dose of 50 mg daily. Max 100 mg/day. | |
| **Duloxetine** | Cymbalta® | 30 mg<br>60 mg | 30–60 mg daily. | Not approved for paediatric use.<br>May cause hepatotoxicity.<br>Contraindicated in glaucoma. |
| | Cymgen® | 30 mg<br>60 mg | | |
| | Yelate® | 30 mg<br>60 mg | | |
| **Dopamine reuptake inhibitors (DRIs)** | | | | |
| **Buproprion** | Wellbutrin® | 150 mg<br>150 mg XL<br>300 mg XL | Start at 75 mg/day, increase to 75 mg twice daily after a week. Continue to increase in 75 mg increments if needed.<br>Maximum of 300 mg/day in divided doses. | Additional indication for smoking cessation. |

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References: **1**. Venlafaxine XR Adco Professional Information. December 2020. **2**. generic.co.za. 2021. Generics Dictionary. Available from: https://www.generic.co.za/frontend/generics?utf8=%E2%9C%93&q%5Bactive_ingredient_nameeq%5D=VENLAFAXINE+HCl. Accessed date: 14 April 2021.

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| **Tetracyclic antidepressants** | | | | |
| **Mianserin** | Lantanon® | 10 mg<br>30 mg | Initially 30–40 mg daily, max 90 mg. | No anticholinergic side effects.<br>Sedating. |
| **Mirtazapine** | Adco-Mirteron® | 15 mg<br>30 mg | Initial dose of 15 mg/day at bedtime.<br>Increase after a week or two to 30 mg/day.<br>Max 45 mg/day. | Very sedating and useful for patients with insomnia.<br>Caution with other sedatives.<br>Useful in patients who experience SSRI-induced sexual dysfunction.<br>Safe drug with low interaction potential, no significant cardiovascular adverse effects in overdose. |
| | Miradep® | 15 mg<br>30 mg | | |
| | Mylan Mirtazapine® | 15 mg<br>30 mg | | |
| | Ramure® | 15 mg<br>30 mg | | |
| | Remeron® | 15 mg<br>30 mg | | |
| | Sandoz Mirtazapine® | 15 mg<br>30 mg | | |
| **Serotonin receptor antagonists and reuptake inhibitors (SARIs)** | | | | |
| **Trazodone** | Aspen Trazodone® | 50 mg<br>100 mg | Initial dose of 100–150 mg/day.<br>Increase after a week or two to 30 mg/day.<br>Max 600 mg/day. | Stop if signs of priapism. |
| | Biotech Trazodone® | 50 mg<br>100 mg | | |
| | Molipaxin® | 50 mg<br>100 mg | | |
| **Selective noradrenaline reuptake inhibitors (NTIs)** | | | | |
| **Reboxetine** | Edronax® | 4 mg | 4 mg twice daily, max 10 mg. | Off-label use for panic disorders and ADHD. |
| **Multimodal antidepressants** | | | | |
| **Vortioxetine** | Brintellix® | 5 mg<br>10 mg<br>20 mg | 10 mg daily, max 20 mg. | |
| **Melatonergic agents** | | | | |
| **Agomelatine** | Valdoxane® | 25 mg | 25 mg daily, max 50 mg. | |

changing to a different antidepressant, or initiating psychotherapy if not already done. If a desirable response is still not observed after 4–6 weeks, it could be considered to combine the current antidepressant with another antidepressant from a different class and mechanism of action. Alternatively, augmentation strategies such as the addition of lithium, or an atypical antipsychotic may be investigated.[44]

### *Paediatric depression treatment*

Fluoxetine is the only agent currently approved in South Africa for the treatment of depression in children. SSRIs may induce mania, hypomania, agitation, sleep disturbances and appetite changes in paediatric patients. The healthcare practitioner, therefore, needs to council parents or caregivers about the adverse effects, safe storage, proper administration, risk of suicide and danger of overdose before initiating pharmacological treatment. TCAs are not considered to be first-line treatment for paediatric patients with depressive disorders, but may be useful in those with comorbid attention deficit hyperactivity disorder (ADHD), enuresis, and narcolepsy. Prior to initiating treatment with a TCA, baseline electrocardiogram (ECG), resting blood pressure, and pulse rate should be determined. Weight and plasma levels should frequently be monitored to avoid toxicity and ensure compliance.[45]

### *Depression during pregnancy and postpartum depression*

Although avoiding the use of medication during pregnancy is preferable, the benefits of prompt medical treatment of major depressive disorder may often outweigh the risks of exposure of the foetus to an antidepressant. Conflicting evidence exists regarding the use of SSRIs during pregnancy and an increased risk of persistent pulmonary hypertension of the newborn. Some rare birth defects have been observed with the use of specific SSRIs; however, no clear evidence indicates that available antidepressants are teratogenic.[46,47] The same risk-benefit considerations should be applied as when treating postpartum depression. For first episodes of depression in postpartum women, 6–12 months of treatment is recommended. Recurrent major depression requires long-term antidepressant treatment.[48]

### *Antidepressants and breastfeeding*

Most antidepressants are likely to be safe for use during breastfeeding. However, studies on the use of antidepressants during lactation have not been adequately evaluated. The same risk-benefit considerations should be applied as when managing depression during pregnancy.[49]

### *Antidepressants and the elderly*

Elderly patients respond to antidepressant agents more slowly, they have a higher incidence of side effects and more drug-drug interactions due to polypharmacy. Antidepressant therapy should be initiated at a lower dose (50% of the normal dose) and slowly titrated until the desired therapeutic effect is achieved. Elderly patients taking SSRIs may develop clinically significant hyponatraemia, including an increased risk of stroke and suicide. Abrupt discontinuation of SSRIs with shorter half-lives, such as paroxetine, may induce withdrawal symptoms which could be confused with recurrence of a depressive episode. Paroxetine discontinuation may additionally cause cholinergic rebound, manifesting with symptoms affecting the gastrointestinal tract. Should nausea and weight loss persist, it is recommended that other treatment options be explored.[50]

## Conclusion

A wide range of effective treatment is available for major depressive disorder. The choice of medication should be guided by a careful assessment of symptoms, patient comorbid psychiatric or general medical conditions, contraindications as well as an analysis of therapeutic benefits and side effects, potential drug interactions and cost. Psychoactive substance abuse and suicide risk should be carefully assessed. Appropriate and up-to-date pharmacological knowledge is necessary for the successful management of depressive episodes.

For a clinical response to become evident, it is necessary to continue treatment for 2–12 weeks at a therapeutic dose. Treatment for major depressive disorder should be re-evaluated if the patient does not have an adequate pharmacotherapeutic response within 6–8 weeks. SSRIs or SNRIs should be considered as first-line treatment for mild to moderate depression. All SSRIs require a wash-out period of at least two weeks before starting other SSRIs, MAOIs or TCAs. SSRIs should not be prescribed within two weeks after discontinuation of MAOI therapy. The possibility of SSRI drug interactions are the highest with fluoxetine, paroxetine, and fluvoxamine and the lowest with escitalopram, citalopram, and sertraline. TCAs are used less frequently as a result of their unfavourable anticholinergic and cardiovascular side-effect profile, attenuated by their considerable toxicity in overdose. TCAs, trazodone, mianserin, mirtazapine and agomelatine are useful in depressed patients with insomnia. Venlafaxine, bupropion, mirtazapine, agomelatine and vortioxetine are less likely to cause sexual dysfunction than SSRIs. The combination of an antidepressant with an antipsychotic is recommended in severe major depression with psychotic features. In the case of a relapse, the antidepressant dosage should be increased, or treatment with another first-line agent with a different mechanism of action should be considered.

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***References available on request.***

# Don't overlook malaria: What the pharmacist needs to know

**L Steyn**

Amayeza Information Services, South Africa

**Corresponding author, email:** lynda@amayeza-info.co.za

## Abstract

The COVID-19 pandemic has shifted the focus away from a life-threatening disease, malaria. As the world opens to travel, the focus on malaria needs to be renewed as more travellers seek advice on malaria prophylaxis. Pharmacists need to be properly informed about malaria to effectively counsel travellers going to high-risk areas. An individual approach needs to be adopted when recommending chemoprophylaxis, taking into account the traveller's risk factors, itinerary and likelihood of adherence to a particular dosage regime.



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## Introduction

Malaria is a life-threatening disease that affects thousands of travellers to, as well as those living in, endemic areas.[1] Globally, 2019 saw 229 million cases of malaria and 409 000 deaths from the disease. However, under-reporting may not paint a true picture of the real figure.[1,2] Between the years 2015 and 2019, South Africa reported approximately 10 000 to 30 000 cases annually.[3]

Pharmacists, being medicine experts and easily accessible, are ideally positioned to advise those travelling to an endemic malaria area of their individual risk of contracting malaria, as well as the measures that can be taken to prevent malaria.[2]

## Understanding malaria

Malaria is caused by a blood parasite of the genus *Plasmodium* and is transmitted to humans via the bite of an infective female *Anopheles* mosquito (the vector).[3,4]

Five species of the *Plasmodium* parasite cause human malaria.[5] The following four species, however, are the most predominant:[5]

- *Plasmodium falciparum (P. falciparum)*
- *Plasmodium malariae (P. malariae)*
- *Plasmodium ovale (P. ovale)*
- *Plasmodium vivax (P. vivax)*

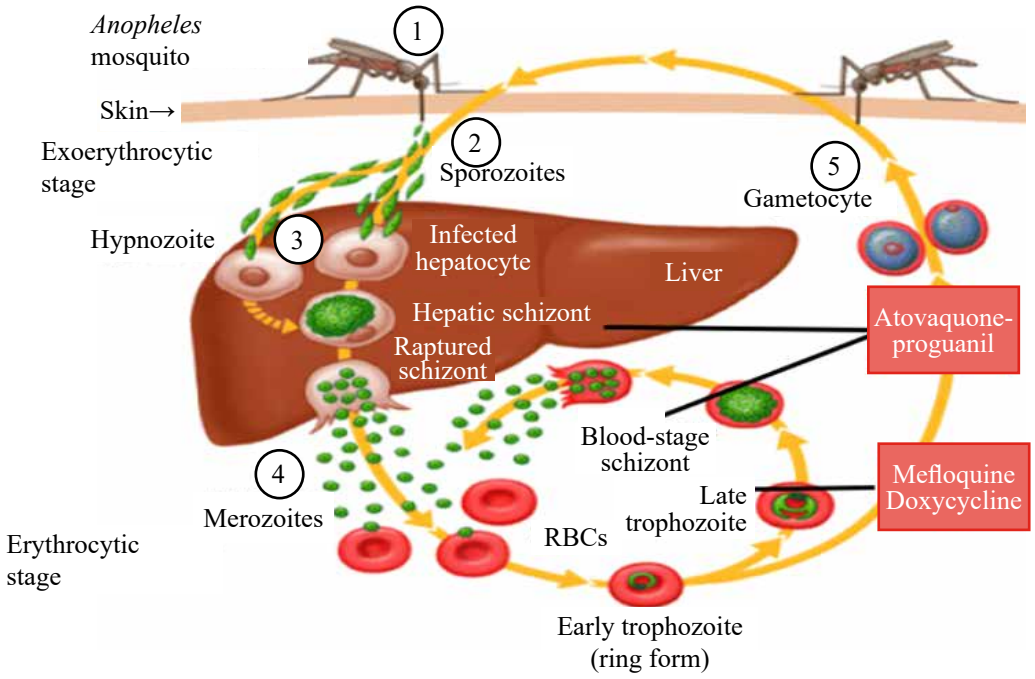


**Diagram 1:** Lifecycle of the malaria parasite[5,6]

*P. falciparum* is responsible for the highest malaria mortality of all the species and is the most common species found in sub-Saharan Africa.[2]

The fifth species, *Plasmodium knowlesi,* originally caused malaria only in monkeys. It is, however, now classified as a human malaria parasite after reports of the disease in humans in Southeast Asia.[5]

The lifecycle of the malaria parasite is described in Diagram 1.[6] Destruction of the red blood cells by the malaria parasites induces the symptoms of malaria. The symptoms usually occur around 10 to 14 days (incubation period) after the mosquito bite. The incubation period may be longer, especially if the traveller took malaria chemoprophylaxis.[5]

1. The infective *Anopheles* mosquito bites a human and injects sporozoites into the blood.
2. The sporozoites migrate to the liver and infect the liver cells (hepatocytes) where they multiply and mature into schizonts (exo-erythrocytic stage).
3. Infections with *P. vivax* and *P. ovale* result in a dormant stage in the liver when their schizonts become hypnozoites. These hypnozoites can remain dormant for months or years.
4. Mature schizonts rupture and release merozoites into the bloodstream (erythrocytic stage).
   - In *P. falciparum* and *P. malariae* infections, all schizonts rupture and all merozoites are released into the bloodstream.
   - In *P. vivax* and *P. ovale* infections, some schizonts rupture, releasing merozoites into the bloodstream, but those that have formed hypnozoites remain dormant. A traveller may relapse when these hypnozoites become active and release merozoites, which restarts the erythrocytic stage.

   Merozoites in the bloodstream invade red blood cells, where they multiply, mature and rupture the red blood cell. Released merozoites invade uninfected red blood cells and the cycle continues until the infected traveller receives treatment or the traveller dies.
5. A few of the merozoites differentiate into gametocytes (sexual blood-stage).
   Gametocytes (male and female) are taken up by an *Anopheles* mosquito during a feed.
   Male and female gametocytes fuse in the mosquito's gut and the resulting sporozoites migrate to the mosquito's salivary glands, where they are ready to be inoculated into a new human host.

## Malaria chemoprophylaxis

Widespread chloroquine-resistant *P. falciparum* malaria has negated the use of chloroquine as an effective prophylactic.[5]

Three chemoprophylactic options are currently recommended in South Africa, namely:[7]

- Mefloquine
- Atovaquone-proguanil
- Doxycycline

Mefloquine requires a prescription (schedule 4), but at the present time is only available for use via section 21.[8,9] Both atovaquone-proguanil and doxycycline are available as schedule 2 products in South Africa, which means that the pharmacist can recommend and dispense either of these to the public for the prevention of malaria without requiring a doctor's prescription.[10]

Malaria chemoprophylaxis can be referred to as either:[5]

- an absolute prevention of infection (causal prophylaxis), or
- a suppression of parasitaemia and its symptoms (suppressive or clinical prophylaxis).

## Blood-stage (suppressive) and liver-stage (causal) prophylaxis

Causal prophylaxis, provided by *tissue schizonticides*, occurs when the drug destroys the exo-erythrocytic forms of the parasite, whereas suppressive prophylactics, known as *blood schizonticides*, act on the erythrocytic stages of the parasite, (where the parasite has already left the liver and entered the red blood cell).[5]

Drugs that act on the liver stage (causal prophylactics) may be discontinued seven days after last exposure.[6]

Drugs that act only on the erythrocytic stages of the parasite (suppressive prophylactics) need to be continued until no more parasites are being released into the blood from the liver (this can occur with *P. falciparum* up to one month after last exposure).[5]

**Atovaquone and proguanil** work synergistically, and are active against the asexual erythrocytic forms of *Plasmodium* (blood schizonticides) as well as the liver stages of the parasite (tissue schizonticides).[5,6] Proguanil works on the pre-erythrocytic intra-hepatic form of the parasite.[5] On its own, proguanil is not able to completely prevent malaria, but when combined with atovaquone, is a causal prophylactic (Diagram 1).[5] The combination is effective against the actively replicating parasites in the liver, and may therefore be discontinued seven days after the end of exposure.[6]

**Mefloquine and doxycycline** are blood schizonticides and therefore work only on the asexual blood stages of the parasite (Diagram 1).[6] Both of these products need to be continued for four weeks after leaving the malaria area as they do not have any effect on the liver-stage parasites, and parasites may still emerge from the liver over this 4-week period.[6,11]

## The A, B, C and D of malaria prevention

While all three available malaria chemoprophylactic agents have equal efficacy in preventing malaria, it is important to note that no one drug is 100% effective in preventing malaria.[2,5] The prevention of malaria involves taking non-drug measures to prevent the mosquito bites as well as, if necessary, tailoring the most appropriate choice of chemoprophylaxis to the individual.[2]

Assessing the risk of malaria and the choice of malaria prophylaxis involves asking the correct questions:[2,5]

## A: Awareness and assessment of the risk

### Where are they travelling to? [5,12]

The latest country-specific malaria maps or guidelines should always be consulted to determine the traveller's risk for contracting malaria.[2]

The following websites provide current maps which may be consulted to determine the risk of malaria in a particular country:

- National Guidelines for the Prevention of Malaria, South Africa
  https://www.nicd.ac.za/wp-content/uploads/2019/03/National-Guidelines-for-prevention-of-Malaria_updated-08012019-1.pdf
- Fit for travel
  https://www.fitfortravel.nhs.uk/home

### Where, when and for how long will they be staying in the malaria area? [5,13]

Malaria risk may also be dependent on the traveller's itinerary.[2]

Table I is a summary of the risk considerations to be taken into account.

**Table I:** Risk considerations[13]

| | |
|---|---|
| **Location** | • Cities – less risk<br>• Camping near a river – high risk<br>• High altitude – less risk |
| **Accommodation** | • Air-conditioned hotels – low risk<br>• Huts or tents – higher risk |
| **Time of year** | • Transmission is lower during dry, cold months; however, in some countries, the risk is year-round |
| **Time of day** | • *Anopheles* mosquito bites between dusk and dawn |
| **Length of stay** | • The risk of malaria is proportional to the length of stay, in other words, the longer one stays in a malaria area, the higher the risk of contracting malaria |

### Who is travelling?

Anyone living outside a malaria area is considered to be non-immune to malaria and is at risk of developing malaria if they get infected.[5] People who once lived or grew up in a malaria endemic area lose their immunity rapidly after moving away from the endemic area and are at risk of contracting malaria when returning to the endemic area.[4]

Certain population groups are at a substantially higher risk for developing severe and complicated malaria.[5] Travel to malaria endemic areas for these groups should be strongly discouraged.[14] If travel cannot be avoided, strict non-drug measures should be adopted and malaria chemoprophylaxis taken.[2]

High risk groups include:[2,5,6,14]

- Pregnant women
  There is an increased risk of serious pregnancy complications if a pregnant woman contracts malaria, such as maternal and foetal anaemia, stillbirth, spontaneous abortion, low birth weight and neonatal and maternal death.
- Infants and children under 5 years of age
  The under 5-year age group is the most vulnerable, and the majority of deaths due to malaria occur in this age group.[5] Complicated malaria characteristics such as severe anaemia, hypoglycaemia and cerebral malaria are more often seen in children than adults.
- Immunocompromised patients
  Immunosuppressed individuals (e.g., patients with HIV/AIDS, those on long-term steroids, or receiving chemotherapy, splenectomised patients) are more vulnerable to severe malaria and death.

## B: Bite prevention (the importance of personal protection methods)

Malaria prevention measures involve a combination of mosquito bite prevention measures as well as appropriate chemoprophylaxis.[4]

Effective mosquito bite prevention measures include:[2,4,13]

- The use of topical repellents, the most effective of which are those containing N,N-diethyl-m-toluamide (DEET), 30–50% (even for pregnant women and children > 2 months of age). DEET should be applied as per manufacturer instructions to all exposed parts of the skin, especially during dusk and dawn when the *Anopheles* mosquito feeds.
- Sleeping under mosquito nets (preferably insecticide impregnated) or in a well-screened air-conditioned room.
- Staying indoors during dusk and dawn, if possible.
- Wearing light-coloured clothing that covers most parts of the body in the evenings.
- Using insecticide sprays or plug-in mosquito repellents indoors.

## C: Chemoprophylaxis

Various factors influence the choice of malaria chemoprophylaxis regime.[13] The prophylaxis should be individualised, taking into account the traveller's itinerary, risk factors for malaria, the age of the traveller, comorbidities and the potential for drug interactions.[5,6]

Table II is a summary of the available chemoprophylaxis regimes.[4-7]

## D: Diagnose promptly and treat effectively

As no antimalarial agent is 100% effective, all travellers presenting with fever or "flu-like" symptoms during or after returning from a malaria area, must seek immediate medical attention to rule out the possibility of malaria.[7] The traveller should be tested for malaria "regardless of suspected COVID-19 condition, (pending COVID-19 tests or even a positive COVID-19 test)." As the symptoms of COVID-19 overlap with the symptoms of malaria, there is a danger

**Table II:** Guidelines for the prevention of malaria[5]

| | Mefloquine | Doxycycline | Atovaquone-proguanil |
|---|---|---|---|
| **Age/weight indications** | Contraindicated in children weighing less than 5 kg | Contraindicated in children under eight years of age | Not for use in children under 11 kg |
| **Dosing and directions** | Weekly dosing<br>1 tablet = 250 mg<br><br>**Adults:**<br>1 tablet weekly (on the same day of each week), starting one week before entering area, once weekly while in area, and continuing for four weeks after leaving area<br>**Children:**<br>Directions as above, with dose according to weight<br>Weight (kg) – Weekly dosage<br>5–20 – ¼ tablet<br>21–30 – ½ tablet<br>31–45 – ¾ tablet<br>> 45 – Adult dose | Daily dosing<br>1 capsule = 100 mg<br><br>**Adults:**<br>100 mg once daily starting one day before entering the area, continuing daily while in the area, and daily for four weeks after leaving the area<br>**Children:**<br>2 mg/kg of body weight at the same intervals as for adults<br>Age years – Weight kg – Dosage<br>8–15 – 31–45 – 2 mg/kg<br>> 15 – > 45 – Adult dose | Daily dosing<br>1 adult tablet = 250 mg atovaquone plus 100 mg proguanil<br><br>1 paediatric tablet = 62.5 mg atovaquone plus 25 mg proguanil<br><br>**Adults:**<br>1 adult tablet daily<br>taken one day before exposure, continued daily during exposure and for seven days after the last possible exposure to malaria<br>**Children:**<br>Weight kg – Paediatric tablets<br>11–20 – 1 daily<br>21–30 – 2 daily<br>31–40 – 3 daily<br>> 40 – 1 adult tablet daily |
| **Most common side effects** | Dizziness, nausea and diarrhoea, insomnia, unusual dreams, headache, mood changes | Skin photosensitivity, gastrointestinal upset, oesophageal ulceration, vaginal candida superinfection | Headache and abdominal pain |
| **Pregnancy and breastfeeding**** | **Pregnancy:** Drug of choice<br>**Breastfeeding:** Insufficient data, WHO states safe to use | **Pregnancy:** Contraindicated<br>**Breastfeeding:** Avoid use unless no other option<br>AAP* states safe to use | **Pregnancy:** Not recommended due to lack of information<br>**Breastfeeding:** Avoid use due to lack of data |
| **Contraindications** | Current or history of psychiatric illness (including depression) or epilepsy<br>Underlying cardiac conduction disturbance or arrhythmia<br>Concurrent use of halofantrine (and other cardiotoxic drugs)<br>Infants weighing less than 5 kg<br>Previous severe reaction to mefloquine | Pregnancy<br>Children under 8 years of age<br>Caution in travellers with myasthenia gravis | Pregnancy (due to lack of data)<br>Severe renal impairment (creatinine clearance of < 30 ml/min) |
| **Drug-interactions (List of examples not exhaustive – please consult guidelines or prescribing information for individual products)** | Amiodarone<br>Beta-blockers (when used for arrhythmia)<br>Digoxin<br>Phenothiazines<br>Pimozide<br>Ciclosporin<br>Halofantrine<br>Dabigatran<br>Rivaroxaban<br>Quinine or quinidine<br>Rifampicin<br>Tricyclic antidepressants<br>Valproic acid | Alcohol<br>Antacids (separate administration)<br>Carbamazepine, barbiturates, phenytoin<br>Ciclosporin<br>Iron (separate administration)<br>Methotrexate (high doses)<br>Isotretinoin<br>Milk and dairy (separate administration)<br>Oral contraceptives (if diarrhoea or vomiting occurs)<br>Rifampicin<br>Warfarin | Protease inhibitors, Zidovudine<br>Magnesium trisilicate (separate administration)<br>Metoclopramide<br>Rifampicin, rifabutin<br>Tetracyclines<br>Warfarin |
| **Special precautions** | Travellers requiring fine coordination | Avoid prolonged, direct exposure to sun<br>Use high SPF sunscreen<br>Take after a meal with a full glass of water<br>Do not lie down for at least one hour after taking | Take with milk or food for better absorption |

*American Academy of Paediatrics
**Babies must receive their own prophylaxis

of missing or delaying a malaria diagnosis, which may be severely detrimental to the traveller.[15] Without prompt, effective treatment, malaria can progress rapidly and be fatal.[2]

## Advice in special situations

***Which malaria prophylaxis is recommended if someone is going to be in a high-risk area for a year or longer?***

The risk of contracting malaria is proportional to the length of stay in the malaria area.[5] The choice of malaria prophylaxis should always be tailored to the individual.[2] There is evidence to support the safety of mefloquine, doxycycline and atovaquone-proguanil for at least two years.[6] In many cases, the justification for long term use is based upon a lack of evidence of harm, as well as the benefit-risk ratio.[5]

People living in endemic areas for long periods of time should be counselled about the importance of not becoming complacent about adhering to malaria chemoprophylaxis and mosquito bite prevention measures.[4]

Recognising the signs and symptoms of malaria is also of utmost importance, as early detection and treatment can save lives. Stand-by antimalarial therapy (SBMT) may be considered for travellers where access to a reliable healthcare facility is not available within 24 hours of onset of symptoms.[5] SBMT does not preclude the need for travellers to seek prompt medical advice.[1]

***What happens if a traveller starts malaria prophylaxis and has side-effects from the medications?[4,5]***

- Antimalarial prophylaxis is generally well-tolerated. Minor side-effects do not warrant a change of medication.
- If side-effects cannot be tolerated before a full course is completed, a switch to another malaria prophylactic agent may be considered depending on certain factors.
- Factors to consider before recommending a switch of medications:
  - Whether or not the traveller is still in the malaria area
  - Which antimalarial the traveller is currently taking (i.e., a causal or suppressive prophylactic)

Table III is a guide for switching prophylactics.

***What should be done if a dose of malaria prophylaxis is missed?***

Drugs with a longer half-life, such as mefloquine, are more "forgiving" in that a day or two late is unlikely to affect blood levels noticeably.[4] The traveller can take the missed dose and resume weekly doses on the original scheduled day of the week. If more than two days late, blood levels may not be adequate. The traveller should take the missed dose and then reschedule the following weekly doses on the same day of the week that the missed dose was taken.[4]

Drugs with a shorter half-life (doxycycline, proguanil) are less "forgiving" and blood levels are not expected to be adequate if the traveller is 1–2 days late in taking the dose. The missed dose should be taken as soon as possible, and the subsequent daily doses adjusted to the new time of day.[4]

**Table IV:** Half-life of various prophylactics[6]

| Drug | Half-life |
|---|---|
| Mefloquine | 2–4 weeks |
| Doxycycline | 15–24 hours |
| Atovaquone | 2–3 days |
| Proguanil | 12–25 hours |

***Does taking malaria prophylaxis "mask" the symptoms of malaria?***

Malaria prophylaxis may delay the symptoms of malaria, as most work as suppressive prophylactics. Milder symptoms due to a delay of onset is due to the disease being milder, not masked. As the disease progresses, the symptoms will present with the same intensity. If a traveller who has travelled to, or is travelling in, a malaria area presents with febrile symptoms, malaria should always be ruled out first, even if it seems longer than the typical time for malaria symptoms to appear.[5]

Appropriate malaria prophylaxis greatly reduces the chances of a high-risk person developing fatal disease. However, it is important to note that no malaria chemoprophylaxis is 100% effective and mosquito bite prevention measures are essential.[1,5] Not recommending malaria prophylaxis to a traveller based on the myth that malaria prophylaxis may mask malaria symptoms, can have detrimental consequences.[5]

**Table III:** Guide for switching prophylactics[5]

| Currently taking | Switching to | Comments |
|---|---|---|
| **Mefloquine** | Doxycycline | Can be done without a washout period |
| | Atovaquone-proguanil | If already in the area, take for 4 weeks (not 7 days) after leaving area (drugs have different action sites) |
| **Doxycycline** | Mefloquine | Not advised – mefloquine needs to be taken a week before entering the malaria area |
| | Atovaquone-proguanil | If already in the area, take for 4 weeks (not 7 days) after leaving area (drugs have different action sites) |
| **Atovaquone-proguanil** | Mefloquine | Not advised – mefloquine needs to be taken a week before entering the malaria area |
| | Doxycycline | Can be done |

## Conclusion

An awareness and understanding of what is required to effectively counsel a traveller going to a high-risk malaria area is essential. Certain population groups, such as pregnant women, infants and children under 5 years of age, splenectomised patients and the immunocompromised are at highest risk of contracting severe malaria, and travel to high-risk areas for these groups should be discouraged. Where travel cannot be avoided, referral to a medical practitioner is advised. Pharmacists should be aware of the symptoms and signs of malaria and any patient presenting in the pharmacy with a fever or flu-like symptoms and a history of travel to a malaria area in the preceding year must be immediately and urgently referred to a medical facility for a malaria test. Early diagnosis of malaria is essential.

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# The need to optimise pharmaceutical education and training for a changing Pharma World

Our local pharmaceutical industry has been gradually moving towards a world-class system. Many forward-thinking South African companies have made great strides in introducing newer production technologies, added manufacturing capability, smart procurement initiatives and advancements in other critical aspects of drug product development, registration and regulation. Despite these advancements, there is still a dire need to close the knowledge and skills gap so that as a country we can become more competitive with our international counterparts to industrialise our pharmaceutical sector and locally produce the majority of our medicines and reduce our dependence on medicine imports.

It is important that we take on a needs-based approach to training individuals for our local pharmaceutical industry with particular attention to the competencies needed to produce the desired pharmaceutical workforce of now and the future. Doing this is fundamentally important for us to reach our goal of growing a more robust pharmaceutical manufacturing sector to further drive economic growth and improvement of our health care system.

In response to this need, Wits Pharmacy in partnership with Aspen Pharmacare has put together a unique series of postgraduate course offerings related to industrial pharmaceutics for individuals who want to further their knowledge and skills in areas of advanced manufacturing, product quality control, the regulatory framework and quality management systems relevant to the pharmaceutical industry of today.

This initiative stems from deliberate and collaborative leadership between academia and industry to pioneer cross-border learning within the Southern African region and develop the human resources needed to service a more industrialised pharmaceutical sector.

A critical component of our country's Universal Healthcare Coverage drive (in terms of medicines access) is for us to produce high quality medicines locally with less reliance on product imports to meet our patient needs. These additional learning initiatives between Aspen Pharmacare and Wits Pharmacy highlight the need for collaborative building of capacity in optimising the skills needed for a thriving pharmaceutical quality system focused on drug product development. The knowledge and skills learnt by individuals on these new courses at Wits Pharmacy positively impacts on them to lead a fulfilling career in the pharmaceutical industry.

With an increasing number of generic manufacturing companies setting up in South Africa, having a critical mass of individuals skilled in these areas in accordance with the South African Health Products Regulatory Authority (SAHPRA) guidelines is critical. As a country, we need to work diligently on closing key gaps in skills and to ensure we reach global standards of pharmaceutical product development with increased manufacturing capacity.

The course also covers the importance of Technology Transfer, Scale-Up, Process Performance, Product Quality Monitoring Systems, Corrective Action/Preventive Action (CAPA) Systems, Change Management Systems and Management Review as part of the initiative to create a unique learning opportunity for individuals to upskill on product and process development for the pharmaceutical industry. The initiative also integrates the elements of commercial manufacturing in line with Quality-by-Design (QbD) principles.

The extraordinary challenges facing the world today, including shifts in job growth and challenges and opportunities brought on by the COVID-19 pandemic, warrant a disruptive re-imagining of how a relevant pharmacy educational offering can boost our economic growth. Learning initiatives such as these go a long way in producing the critical mass of individuals needed to realise a more industrialised and sustainable future-proof pharmaceutical manufacturing sector in the country.

For further information, contact Professor Yahya Choonara – Chair and Head of the Department of Pharmacy and Pharmacology at Wits: yahya.choonara@wits.ac.za.

# Empowering pharmacy students and practising pharmacists to become vaccinators during the COVID-19 pandemic and beyond

**Razeeya Khan, Ané Orchard, Muhammed Vally**
Department of Pharmacy and Pharmacology, Faculty of Health Sciences, University of the Witwatersrand, South Africa
**Corresponding author, email:** muhammed.vally@wits.ac.za

Data suggests that patients are as likely to accept an immunisation recommendation from a pharmacist as they are from a physician or a nurse.[1] Pharmacists are generally in an ideal position to recommend immunisation due to the large foot traffic which frequents the pharmacy every day, as it is estimated that 55% of adults frequent a pharmacy at least once a week.[2,3] When pharmacists are added as vaccine providers, this results in increased access and higher rates of adult vaccination.[4-9]

Considering the above, the Division of Clinical Pharmacy at the University of the Witwatersrand set in motion two different plans. One was to develop an immunisation and injection technique course for pharmacists established in practice wanting to immunise patients, both in terms of the EPI and to provide adult vaccinations for diseases such as pneumococcal disease, influenza and COVID-19. This competency course was developed by the academic staff members in the clinical pharmacy division and is already approved through the University of the Witwatersrand. The course meets all the necessary training requirements as stipulated by the South African Pharmacy Council (SAPC). The course is currently being assessed by the South African Pharmacy Council and is awaiting accreditation. On accreditation of the course by the SAPC, participant pharmacists will complete the majority of the course material online and will attend face-to-face training for the practical component, which includes injection techniques and anaphylaxis management. Participant pharmacists will be required to complete a written assessment and an assessment of their injection technique. The post-assessment component of the course includes the administration of intramuscular and subcutaneous injections under the supervision of a nurse, trained pharmacist, PCDT pharmacist or doctor. Participants will submit their completed immunisation record to the University for assessment, after which a certificate of competency will be issued. The certificate can then be used by the participants to apply for a Section 22 A(15) permit that will enable them to provide immunisation and injection services to the community.

The second intervention was to continue the training of the current final year pharmacy students so that they could contribute to the COVID-19 vaccination drive in South Africa. At the University of the Witwatersrand, the final year students already have the underpinning theoretical foundation required from the medical microbiology, clinical pharmacy, pharmaceutical microbiology, and pharmacy practice courses. A practical component to put the theory into practice was required.

The clinical pharmacy division utilised the existing Screening and Testing Programme for Pharmacy Students (STEPPS) infrastructure. Students had to complete a 4-hour set of online lectures and watch specially developed injection technique videos. After completing this, students then attended 4-hour training sessions, where they first practiced vaccination on task trainers prior to administering normal saline injections intramuscularly to each other in the deltoid, under direct supervision. The students were then required to complete an allergy and anaphylaxis high fidelity simulation. Students who volunteered to be vaccinators, completed the COVID-19 vaccinators training from the Department of Health. The list of student volunteers who completed both the divisional training and the National Department of Health training was submitted and they were subsequently assigned to a vaccination site, where they could work under direct supervision.

The pandemic required a rapid response and the clinical pharmacy division at the University of the Witwatersrand promptly put these measures in place to contribute towards the roll out of the COVID-19 vaccination programmme.

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# The mind outside the mind

**Shawn Zeelie**

President, SAAHIP

*Shawn Zeelie*

The mind is a powerful thing. During the month of October, we focussed on mental health awareness. What determines if a person is mentally ill and what determines if the person is not? The definition of mental illness varies from person to person, however, if a person's thinking process is off balance, you are more than likely going to find a mental illness. It is natural to occasionally experience suspicions, a loss of thought and the inability to say what is on your mind, as well as other symptoms such as anxiety and depression. However, if these symptoms are ongoing, and interfere with your ability to cope with daily life, it is important to seek help.

The experts in mental illness often interchange the terms mentally ill and disorders since one term means that a patient has a disturbance in normal patterns and the other means that a patient will need ongoing treatment for the disturbances. The *Diagnostic and Statistical Manual of Mental Disorders* (DSM) will assist in defining the various mental illnesses as well as how to manage the condition.

Most of our patients who are on neuroleptic medicines suffer from either extrapyramidal side effect or tardive dyskinesia. An interesting method to distinguish between the two, as explained in the DSM, is the Abnormal Involuntary Movement Scale (AIMS). After interviewing the patient, the scale will help to distinguish between the two and a pharmacist will be able to assist in managing the patient accordingly. This makes it easier in deciding which medicines can be given to the patient.

Especially during the current COVID-19 pandemic, we as healthcare professionals are faced with a lot of challenges. Whether it be the stresses of having to supply stock of which there is a shortage, or the amount of critically ill patients we see. All of this contributes to our mental state. We might find ourselves a bit short-tempered, as well as frustrated. This may result in our feeling depressed. You are not alone, there are various support mechanisms which will assist in coping with the current emotional strain we are all going through. There are healthcare workers care centres and various support groups. If the pressure becomes too much for you, feel free to contact them. Most people say it is a weakness to seek help, but on the contrary, it takes a tremendous amount of strength and courage to ask for help.

# HIV and TB co-infection in children

**Shawn Zeelie**

Robert Mangaliso Sobukwe Hospital, Kimberley, South Africa

## Abstract

The epidemiology of tuberculosis is adversely impacted by the human immunodeficiency virus (HIV) co-infection. HIV-infected patients are more prone to opportunistic infections, most commonly tuberculosis, and the risk of death in co-infected patients is higher than in those without HIV due to the impaired cellular immunity and reduced immunological response in HIV-infected patients.

## Introduction

The management of HIV infection has changed significantly over the last 10 years, with the development of new antiretroviral medications, including better formulations and fixed-dose combinations. Since the introduction of earlier treatment as well as pre-exposure prophylaxis, there has been both a significant reduction in HIV-related illnesses and an increase in the proportion of patients who are virally suppressed. This article aims to improve pharmacists' understanding of the particular needs of the HIV/TB co-infected child, with reference to updated treatment guidelines, and to emphasise the role that pharmacists can play in the care of these patients.

## Epidemiology and pathophysiology

HIV is transmitted through contact with the blood, semen, vaginal secretions, breast milk, saliva, or exudate from wounds or skin and mucosal lesions of someone infected with the virus.[1] The main means of transfer of the virus is directly via bodily fluids.[2] However, the primary paediatric route is vertical transmission from mother to child. Vertical transmission rates in Africa vary from 25–52%. Prevention of mother-to-child transmission (pMTCT) interventions can decrease this percentage to less than 2%.[3]

Vertical transmission can occur before birth (intrauterine), during birth (intrapartum), or after delivery (usually via breastfeeding). As early as 10 weeks' post-conception, intrauterine transmission can be detected by polymerase chain reaction (PCR) testing of foetal tissue. About 30–40% of newborns are infected *in utero*, if the mother is not successfully treated with antiretrovirals (i.e. is not virally suppressed). Detection of the virus soon after birth correlates with early onset of symptoms and rapid progression to AIDS, consistent with more long-standing infection during gestation. Nonetheless, it is estimated that 60–70% of neonates do not have detectable virus before one week of age. The mechanism of transmission appears to be exposure to infected blood and/or cervico-vaginal secretions in the birth canal.[3] Transmission can occur transplacentally or perinatally.

The least common route of transmission is via breast milk. Both free as well as cell-associated viruses have been detected in breast milk from HIV-infected mothers. The risk of transmission via breast milk is 14% in children whose mothers were HIV infected before pregnancy and 29% in children whose mothers were infected postnatally, as the viraemia experienced by the newly infected mother increases the risk of transmission.[3] Other risk factors include preterm delivery (< 34 weeks), a low maternal CD4+ cell count and the use of illicit drugs. The most important variables appear to be prolonged (more than 4 hours) ruptured membranes and a birth weight less than 2 500 g. Each of these factors doubles the transmission rate of the virus. The transmission rate can be decreased by 87% by caesarean section delivery, in combination with zidovudine therapy for both the mother and infant.[3] There is an increased rate of transmission in women with advanced disease.[3] If the mother is not receiving antiretroviral treatment (either for pMTCT or as combination antiretroviral treatment [cART]), the risk of transmission is 25–35%.[1]

Access to ART varies dramatically, with only 21% of paediatric patients accessing treatment, compared with 55% of adults.[4] Without treatment, 50% of African children living with HIV will die before their second birthday. The prevalence of HIV among children infected with TB is difficult to estimate due to problems with diagnosis, under-ascertainment as well as selection of study populations. It has been estimated by the WHO that the prevalence ranges from 10–60%. This prevalence differs depending on the background rates of HIV as well as the economic status and education level of the population.[2]

The prevalence of TB in HIV infected patients differs according to whether or not the area is a TB endemic area and whether or not ART is freely accessible. Under-ascertainment as well as difficulty in diagnosing the patient also remains a problem. In a South African retrospective study, the incidence of TB in HIV infected children was estimated at 5 per 100 child-years among HIV-positive children receiving HIV care. Although more and more of the population is gaining access to ART, the prevalence of TB remains higher in HIV co-infected children than in HIV-uninfected children.[2]

The pathogenesis of TB is also affected by HIV. In people living with HIV there is a 6–30 fold increase in the chances of developing HIV. The chances of developing TB increases when the patient has a lower $CD_4$ count or is living in a high TB incidence area, for example.[2]

## Clinical presentation

Often a child is not suspected of having HIV until they develop symptoms of the disease. This can vary according to age and each child can present differently. Symptoms may result from HIV or from opportunistic infections. Common presentations include lymphadenopathy, white plaques due to oral *Candida*, painful rash

due to *Herpes zoster*, diarrhoea, fatigue and fever with intermittent sweats.[1] Most commonly, children are detected through a failure to thrive (FTT), which is the failure to gain weight or grow according to standardised growth charts. In addition, neurological complications may be detected, such as seizures, difficulty with walking or poor performance at school. There may be frequent childhood illnesses such as ear infections, colds as well as diarrhoea. When HIV progresses further, the incidence of opportunistic infections increases. These infections include *Pneumocystis jirovecii*, cytomegalovirus, lymphocytic interstitial pneumonia (LIP), oral *Candida*, diaper rashes, tuberculosis as well as meningitis.

The first signs and symptoms may be subtle and non-specific, e.g. lymphadenopathy, hepatosplenomegaly, FTT, chronic or recurrent diarrhoea, interstitial pneumonia or oral thrush. If these are recurrent, HIV is more likely. In Africa, chronic diarrhoea, wasting, as well as severe malnutrition are the predominant signs/symptoms. In children, certain signs and symptoms are more commonly found than in adults. These include recurrent bacterial infections, chronic parotid swelling or LIP. Some children experience early onset progressive neurological deterioration.[3] In TB co-infected patients, cough for more than 1 610 days, fever for more than 2 weeks as well as weight loss and FTT may be present.

## Criteria/diagnostics

As per current South African standard treatment guidelines,[5] the criteria for testing for HIV in children are as follows: all infants/children accessing care should have their HIV status determined. However, those who have tested positive or are already on ART should not be tested again. Table I explains the role of PCR and rapid antibody tests in the management of infants and children.

In addition, mothers who tested negative in pregnancy, should have their HIV status determined three-monthly whilst breastfeeding. The guidelines emphasise that breastfeeding should be encouraged in all mothers with HIV-infected children, 2 years or longer, as in HIV-unexposed children. Weaning foods can be introduced from 6 months of age. Importantly, providers are encouraged to ask about TB contacts and TB symptoms in all children and their caregivers at every visit.

If ART is initiated in a child on TB treatment, liver enzymes should be checked at initiation. In addition, TB should be excluded in all patients before starting ART. This can be done by means of a careful history of TB contacts, clinical examination, chest X-ray, tuberculin skin test (TST), or lateral flow urine lipoarabinomannan (TB-lam), *M tuberculosis* PCR test and mycobacterial culture (where TB disease is suspected on clinical or radiological grounds).

TB prophylaxis should be given to all HIV-infected children exposed to a close contact with an infectious pulmonary TB case, or who are newly found to have a positive TB-lam or TST, but in whom no evidence of TB disease is present. The standard dose is isoniazid 10 mg/kg/dose (up to a maximum of 300 mg) once daily for 6 months. Importantly, the course needs to be repeated if an HIV-infected patient, irrespective of age, is re-exposed to a TB contact at any point after completing TB treatment or prophylaxis. However, if the patient has been exposed to a known drug-resistant TB case, then expert advice is needed on the choice of prophylaxis.

**Table I:** HIV testing recommendations for infants and children[5]

| **Recommended intervals for infant and child testing** | |
|---|---|
| **HIV PCR test** | **Rapid HIV antibody test** |
| **At birth**<br>• All HIV-exposed neonates<br>**At 10 weeks**<br>• All HIV-exposed infants<br>**At 6 months**<br>• All HIV-exposed infants<br><br>Repeat HIV PCR testing at 10 weeks and 6 months should be done on all HIV- exposed infants with a prior negative or indeterminate HIV PCR<br><br>Any infant with a positive birth HIV PCR should be urgently initiated on ART as per section 9.1.2: The HIV-Infected Neonate | **At 18 months**<br>• Universal HIV testing at 18 months (HIV rapid test for ALL infants regardless of HIV exposure, except in those who previously tested HIV-positive and are on ART)<br><br>**Note:** Patients already on ART should not have a repeat HIV antibody test<br><br>**Breastfed infants: (6 weeks post cessation of breastfeeding)**<br>• All HIV-exposed infants – age appropriate:<br>< 18 months old – do an HIV PCR<br>≥ 18 months old – do a rapid HIV antibody test (confirm HIV test in children between 18–24 months with an HIV PCR)<br><br>**HIV testing should be offered to all children as well as their family and caregivers.** |

The timing of TB and ART is critical, and depends on when each diagnosis is made. If a child is diagnosed with TB and HIV, but is not yet on ART, then the TB treatment should be commenced first, and ART initiated after 2–4 weeks. However, in children with TB meningitis, ART must only be initiated after 4 weeks regardless of CD4 count, in order to avoid immune reconstitution inflammatory syndrome (IRIS). If a child is diagnosed with TB when already on ART, TB treatment can be commenced immediately, with due regard for possible drug interactions. There may be a need for ART dosage adjustments. For example, if a child is to receive a rifampicin-containing TB regimen and is taking dolutegravir, the ARV should be dosed twice daily. No dose adjustments are needed in children receiving efavirenz, abacavir or lamivudine. Boosted ritonavir dosing is needed in children treated with lopinavir/ritonavir. However, double-dosing the lopinavir/ritonavir solution in young children is not recommended.

All children on TB treatment and ART should receive pyridoxine to prevent neurological adverse effects.

## Goals of therapy

The goals of therapy in the child with TB/HIV co-infection vary. The long-term goals with ART are to prevent progression of the disease, including opportunistic infections, and to suppress viral replication. Other goals include avoiding adverse effects from the ART and interactions with other medication. The goals of TB treatment are to cure the infection, while avoiding adverse effects and drug interactions, and to prevent the development of complications. Preventing recurrent or reactivation of TB are longer-term goals.

## The role of pharmacists

Pharmacists can play a vital role in optimising HIV treatment outcomes in numerous ways and in all medical settings, such as ensuring patients are taking a complete and appropriate regimen, recommending alternative therapy, dose or formulation adjustments, mitigating drug-drug interactions, and modifying drug schedules to optimise absorption. Current literature suggests a profound impact on improving safety in HIV patients through pharmacist interventions, via medication error prevention and daily monitoring. Retrospective studies have seen rates of antiretroviral stewardship interventions for medication errors related to antiretrovirals increase from 16% to 52%. Various methods of stewardship interventions have been utilised, including prescriber and pharmacist education[6-9]

## Conclusion

There is still much left to be done, even with the great progress that has been achieved over the recent years. Although there are fewer HIV diagnoses and improved viral suppression, globally, the world has yet to meet the UNAIDS 90-90-90 targets. The risks of medication errors are high in children being treated for HIV/TB co-infection, due to the multiple agents having to be used simultaneously. However, this provides a great opportunity for pharmacists to optimise and improve the medication use process. Pharmacists can play a key role in the management of patients on ART and TB treatment, ensuring patient safety and optimal patient care. With a variety of methods to reduce medication errors, such as use of computerised order entry sets, provider education, and prospective feedback, pharmacists can continue to work to make an impact in advancing HIV/TB patient care and supporting the continuum of care.

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# COP26 and green pharmacy – ICPA position paper

**Dr Sham Moodley**

***Paris was all about commitments, Glasgow has got to be about action!***

In adopting the FIP Development Goal 21 (Sustainability in Pharmacy) ICPA has been driven to action in the three key identified areas. The first is our response to ***disasters and pandemics*** through both the COVID-19 action programme, including our COVID-19 testing of healthcare workers in 2020 and, in 2021, through the extensive COVID-19 vaccination programme provided through community pharmacy. ***Sustainable services*** introduced as part of our three-year planning cycle includes discussion with payers and Government on a fair and transparent remuneration model, development of pharmacy initiated services in both communicable and non-communicable diseases such as Pharmacist Initiated Management of Anti-retroviral Therapy (PIMART), Kamba Ya Shanga (asthma) programme, Diabetes Registry Project, Outcomes Measures and Reporting (OMR), Donor Recruitment Centre (DKMS Africa) for the fight against blood cancer and our AMR education.

The third in Goal 21 and current topic of worldwide interest (COP26) is ***environment and planetary health*** (Climate Change). Over the years, we have dabbled in mini projects such as medicine disposal, empty inhaler return, needle disposal and a move away from plastic bag usage. Pharmacy and medicines have a huge environmental impact starting from the manufacturing plant, storage and disposal, distribution chain all the way into the hands of the patients. Further to that, we have a responsibility to influence Government Policy, contribute to enacting laws, creating a green working environment, influencing our partners, and educating the communities we work in. Studies have indicated a significant concentration of pharmaceuticals in sewerage, waste-water treatment, and surface water.[1] Most of these are released from production facilities, excretion from humans and animals using medicines and inappropriate disposal of medicine waste including unused medicines.[2]

Daughton[3] proposed the need for green pharmacy policy that appropriately assessed, anticipated, and managed pharmaceuticals, a cradle to grave concept. It is the intention of ICPA to create a series of partnerships to ensure we have a sustainable approach to pharmaceuticals as we too become early adopters of the FIP Green Pharmacy Policy.[4] There are a number of notable green projects in the South African healthcare industry, participants include manufacturers, distributors, green hospitals and schools of pharmacy. Performing a risk assessment of activities and issues associated in the pharmaceutical process, measuring its impact on the environment, and providing solutions to mitigate the environmental risk is the direction the ICPA Board intends taking. Designing key indicators and providing annual assessments of progress will become a measure of our success.

It has been recognised that climate change has a direct and indirect influence on the health of our patients/communities through extreme weather patterns having an impact on food security, flooding, drought, infectious disease patterns, and respiratory diseases via air pollution (Kirsty Reid – European Federation of Pharmaceutical Industry and Assoc [EFPIA]). The COP26 agenda in Glasgow is a firm drive to encourage a ***net-zero carbon footprint*** operation. The global pandemic has also created an opportunity for our industry to rethink the business-as-usual concept. There is also a business case being made that climate change principals are based on being less wasteful with energy consumption, production waste, transportation, water consumption – all of which leads to better financial performance. The NHS in the UK[5] has set out an ambitious plan to become the world's first net-zero National Health Service identifying that medicines accounts for 25% of total emissions from the health service. Based on this assumption, pharmacy in South Africa has a huge role to play in assisting Government achieve its targets.

The IPCC Sixth Assessment Report Summary[6] (to which South Africa has drafting authors François Engelbrecht and MS Monteiro and contributing author Rondrotiana Barimalala) indicates that we need to halve greenhouse gas emissions between 2020 and 2030, reverse nature loss in order to reach net zero and limit global warming to 1.5 °C. Time is running out, and every fraction of a degree threatens to cause more death and economic destruction. Minister Barbara Creecy (Forestry, Fisheries and Environment-

SA) said, "The Glasgow outcome should be a package deal that advances the negotiations and all three aspects of the Paris Agreement, namely ***mitigation, adaptation*** and the means of ***implementation*** of climate action. South Africa stands ready to play a constructive role for the success of COP2."[7] Pharmacy needs to focus on the practical solutions of mitigation, adaptation and implementation. A good example is the implementation of a better ordering system in 3 800 pharmacies across the country, removing the need for "just-in-time deliveries" and eliminating the need for 3–5-times a day delivery. Imagine the impact of this number of reduced deliveries and its contribution to the ***net-zero carbon emission***. There are many examples of this type of initiative that will satisfy the goals of COP26 and make business sense in medicine supply. ICPA will map out the process.

**"This is not a drill. It's code red for the Earth. Millions will suffer as our planet is devastated — a terrifying future that will be created, or avoided, by the decisions you make. You have the power to decide."**

*Greta Thunberg*
(Swedish environmental activist)

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# Letter to the Editor

## ENGAGE

There comes a time in one's life where a decision to pour your life out to and for something is all you have to do. Delivering health care is fast transforming in more or less the same way as all other industries. The systems, platforms, requirements, technical skills and competencies as well as polity and legal framework around how things ought to be done is rapidly changing faster than we can blink. You need not be caught off-guard debating how things used to be. You cannot afford to be found wanting. What got us here will not take us there. This means there is a need for a mental and leadership shift. The International Pharmaceutical Federation (FIP) launched and published 21 the FIP Pharmaceutical Workforce Development Goals (PWDGs) that seeks to align pharmacy with the United Nations' Sustainable Development Goals, thus positioning pharmacists not as local but global champions towards "transforming global pharmacy"[1] These goals have the potential to position a pharmacist beyond currently recognised power, in primary healthcare, hospital care, training and research, business and other innovative healthcare delivery approaches in existing and emerging markets. However, this will require a generation of bold, decisive leaders and innovators who are ready to go beyond the call of duty to secure a seat in the king's table. Martin Luther King Jr summed this up in saying "if a man hasn't found something he will die for, he isn't fit to live." Well, that's rather graphic, isn't it? Maybe if I put it in the poetic words of spiritual activist and author, Mariane Williamson made famous by Nelson Mandela it will make sense:

*Our deepest fear is not that we are inadequate.*
*Our deepest fear is that we are powerful beyond measure.*
*It is our light, not our darkness*
*That most frightens us.*

*We ask ourselves*
*Who am I to be brilliant, gorgeous, talented, fabulous?*
*Actually, who are you not to be?*
*You are a child of God.*

*Your playing small*
*Does not serve the world.*
*There's nothing enlightened about shrinking*
*So that other people won't feel insecure around you.*

*We are all meant to shine,*
*As children do.*
*We were born to make manifest*
*The glory of God that is within us.*

*It's not just in some of us;*
*It's in everyone.*

*And as we let our own light shine,*
*We unconsciously give other people permission to do the same.*
*As we're liberated from our own fear,*
*Our presence automatically liberates others."*[2]

Given the landscape of the practice of pharmacy, taking a back seat will not help. Deciding to take to social media to lament the ordeal you are facing with like-minded complainants will not open a door for help. Instead, it may keep you locked in a depressed and unsatisfied room of disappointment when you realise that nothing changes when you don't change and change them. How pharmacists responded to the changes brought about by COVID-19 is a clear indication of our current mental framework. How we will continue to dispense ourselves over the next decade will depend on the price we are willing to pay now. The price to lead change or the price to maintain the status quo have been set on the table for the profession to choose what befits our role, expertise and relevance.

This letter is a call to action, to go to the lab, to your research office, dispensary, ward, classroom, consulting room with a different mental makeup of one who unapologetically owns the space and formally and solidly build on ground and a pharmaceutical expert, one whose role forms the backbone of healthcare. One who delivers healthcare as a calling with reward. Engage the debate in all platforms that offer your voice an audience that is able to take the action in heed of your plea. The time is now. The time is now for pharmacists, individually or collectively to lead, in the space where you are. Be the change you want to be.

**Nhlanhla G Mafarafara**
*BPharm. MPharm*

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# Letter to the Editor

Hi Lorraine,

Hope you and your family are all keeping well and safe.

I was very interested to read in the May/June edition of the SAPJ, only received last week, that the Society, as structured now, was founded 75 years ago in 1946, and the Journal in 1934. This got me thinking of all the people I met during my pharmaceutical political career.

I remember meeting William Patterson, at one of my first Southern Transvaal branch meetings, creator of the original PSSA constitution and Editor-in-Chief of the SAPJ from 1934 until 1963, and Aaron Kramer, editor of the Journal until about 1970. He always arrived at meetings with his little suitcase with all his drafts for the next Journal. I would like to endorse what Susan Buekes (Wormald), my colleague from Durban Tech, said about our being informed of the passing of our colleagues.

I entered the profession in January 1953, but only qualified as a pharmacist in April 1960, having got a supplementary exam along the way. I was one of the last to graduate under the old regulations, three years of apprenticeship and two years of college. In 1958, the system was switched to three academic years. I was forced into pharmaceutical retirement in 2003, when I emigrated to Canada, and was refused employment as a pharmacist.

Thanks and appreciation to all your team for the excellent journal you publish. Keep up the good work.

Regards

**Bernard Lapidus** FPS

P.S.

Wishing you and all your family and staff at Head Office and the Branches, a merry Christmas and all the best for a COVID-free 2022.

# Obituaries

## Gavin Donald Bamber

### *15 June 1936 – 11 October 2021*

Gavin graduated from Rhodes University with a BSC (Pharm) degree in 1965 having served as Chairman of RUPSA in 1963/1964 and was a member of the SAPSF Executive in 1964/1965.

On 5 March 1973, Gavin joined the PSSA and was soon elected to the Branch Committee. In 1976 he was elected as Branch Chairman and represented the Branch on the National Executive Committee for many years serving that body as Chairman of the Constitutional and Contracts Committee at various times. Gavin was Vice President of the Society from 1981 to 1984 and served as its President in 1985.

He was also elected as a member of the South African Pharmacy Council where he served the profession with distinction.

For his exceptional service to the profession over many years Gavin was awarded Fellowship of the Society in 1968 and was later recognised with Honorary Life Membership of the Society. Very few members of our Society have achieved what Gavin achieved in a variety of capacities and areas of interest for the benefit of the profession.

Gavin became very interested in computerisation and was instrumental in the computerisation of the MediKredit Checking Office system the establishment of the Computerised Pharmacy Systems a company associated with the Scriptmaster dispensing system.

Four members of the Bamber family became pharmacists – Bill, the father of Gavin and Neville, and Carolynne – Neville's daughter.

Gavin leaves his wife Sarah and children Caroline, David, and Victoria, to whom we send our sincere condolences.

We have lost an exceptional friend of the profession – may he rest in peace.

# George Neville Lyne

## *10 April 1935 – 29 August 2021*

Neville Lyne was a long-time friend and colleague, who had a varied and interesting career. From 1953–1960, he was employed in various community pharmacies in Durban, where he also attended the Pharmacy School, after which he completed his pharmacy apprenticeship.

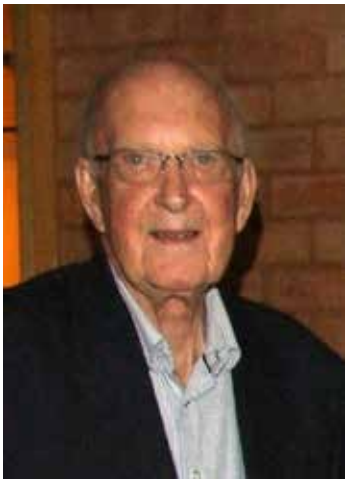
He then changed direction, joining Scherag (Pty) Ltd as a professional services representative (rep) for the extensive Natal, east Griqualand, Transkei, southern Orange Free State (OFS), and Swaziland regions. From 1961 to 1970, Neville was transferred to the Scherag Head Office in Johannesburg, as understudy to the Pharmaceutical Director, Dr Mike Tonkin. He was later promoted to National Sales Supervisor of the White Laboratories division, and subsequently to National Sales Manager for the Schering Corporation division, for South Africa.

My personal association with Neville started in February 1963, when I joined Scherag as a medical rep, travelling across the (then) southern and eastern Transvaal, and far northern OFS.

From 1971, Neville's responsibilities were expanded internationally to include Mozambique and Angola, and later he was promoted to Marketing Planning Manager at Schering Plough European headquarters, Switzerland, where he was responsible for corticosteroids, antihistamines, and gastrointestinal medicines for western Europe, excluding France and west Germany but including Scandinavia, and in addition, Middle Eastern countries and Africa South of the Sahara. He was eventually transferred to Belgium as Marketing Manager.

In 1981, Neville returned to Johannesburg to take up the position of Head of Communications and Marketing at the PSSA national office. Together with Oppel Greeff and Hugo Durrheim, Neville introduced CPD courses for members. He also organised and managed the AGMs and conferences, among other responsibilities. He was appointed Chairman of the hugely successful and popular Pharmacy Professional Awareness Campaign (PPAC), promoting pharmacy to the general public via print, radio, and TV media, while also supervising the office of the SA Pharmaceutical Journal in Braamfontein, during the terms of several PSSA Presidents.

In 1991, in conjunction with Colin Stanton, Neville conceptualised and introduced Insurance Advisor, the Professional Indemnity



Insurance Plan (PIP) for PSSA members. This was originally managed by the Southern Gauteng (SG) branch of the PSSA but is now run by the Professional Provident Society in partnership with PSSA National.

As a token of appreciation for exceptional service to pharmacy and the PSSA, as a non-pharmacist and non-member, in May 1995 Neville was awarded Honorary Fellowship of the PSSA. In April 2000, he retired from full-time activities but continued to manage the PIP until this was transferred to the National Office.

In 2004, the SG branch invited Neville to take up the position of Professional Officer, and to manage their CPD programme, in a part-time capacity; he was also invited to join the Editorial Board of The Golden Mortar (GM), the SG Branch Newsletter. From 2014, Neville managed and arranged the Branch's Clinical CPD programme, continued as Professional Officer, and since 2018 acted as Publishing Coordinator of The Golden Mortar, even after his retirement from office in 2019. The high standard of the GM is the legacy that Neville has left.

My overall impressions of Neville, the man, are of his competency, professionalism, clear thinking, dedication, his sage advice, his co-operation, his gentlemanly manner and wry sense of humour, and the respect which he was shown.

Our sincere condolences to Eleanor, Stuart and Nikki. MHDSRIP.

**Dave Sieff**

Calpol

# STARTS TO WORK ON FEVER IN 15 MINUTES[1-3]

gsk

## CALPOL PAEDIATRIC IS SUITABLE FOR YOUR CHILD BECAUSE:

- Gentle on tiny tummies[1,4]
- Has an suitability profile among children's OTC analgesics/antipyretics[5,6*]
- Has fewer drug-drug interactions than ibuprofen[6]


Formulated especially for children

## REMIND YOUR PATIENTS ABOUT THE IMPORTANCE OF DOSAGE BY WEIGHT

### CHILDREN'S DOSAGE

| CALPOL DOSAGE AND DIRECTIONS FOR USE: | | |
|---|---|---|
| **Age** | **Weight** | **Dose** |
| Under 3 months | Not recommended | |
| 3 - 6 months | 6 - 8 kg | 3.75 ml |
| 6 - 24 months | 8 - 12 kg | 5 ml |
| 2 - 4 years | 12 - 16 kg | 7.5 ml |
| 4 - 6 years | 16 - 20 kg | 10 ml |
| SHAKE THE BOTTLE BEFORE USE. | | |

Match the child's weight to the chart above. If the weight is not known, then match the age of the child.

*when used as directed


References: **1**. Temple AR, Temple BR, Kuffner EK. Dosing and antipyretic efficacy of oral acetaminophen in children. *Clinical therapeutics*. 2013 Sep 30;35(9):1361-75. **2**. Wong A, Sibbald A, Ferrero F, Plager M, Santolaya ME, Escobar AM, Campos S, Barragán S, González MD, Kesselring GL, Fever Pediatric Study Group. Antipyretic effects of dipyrone versus ibuprofen versus acetaminophen in children: results of a multinational, randomized, modified double-blind study. *Clinical pediatrics*. 2001 Jun 1;40(6):313-24. **3**. Mahar A.F, *et al.* "Tepid sponging to reduce temperature in febrile children in a tropical climate. *Clinical pediatrics* 33.4(1994):227-231. **4**. De Martino M, Chiarugi A. Recent advances in pediatric use of oral paracetamol in fever and pain management. *Pain and therapy*. 2015 Dec 1;4(2):149-68. **5**. World Health Organisation. Pocket Book for hospital care of children, 2013. Available at: http://www.who.int/maternal_child_adolescent/documents/child_hospital_care/en (accessed 27 September 2017). **6**. WHO Guidelines for the Pharmacological Treatment of Persisting Pain in Children 2012. Available at: http://whqlibdoc.who.int/publications/2012/9789241548120_Guidelines. pdf (accessed September 2017).