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SA Pharmaceutical Journal

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NEW

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Each 1 ml contains 0,6 mg of ipratropium bromide and 0,5 mg of xylometazoline hydrochloride for symptomatic relief with[1]:

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- Runny nose
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Reference: 1. OTRIVIN PLUS Nasal Metered-dose Spray (Solution) package insert February 2021.

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- SA Association of Hospital and Institutional Pharmacists
- SA Association of Pharmacists in Industry

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

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

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

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

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

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

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Have you seen the black swan?

Natalie Schellack

The writer Nassim Nicholas Taleb popularised the concept of "black swan" events in his book, *The Black Swan: The Impact Of The Highly Improbable*. The essence of Taleb's work is the world is severely affected by events that are rare and difficult to predict, with consequences that could be positive or negative. Taleb provided the following definition before an event can be classified as a black swan event:

"First, it is an outlier, as it lies outside the realm of regular expectations, because nothing in the past can convincingly point to its possibility. Second, it carries an extreme 'impact.' Third, in spite of its outlier status, human nature makes us concoct explanations for its occurrence after the fact, making it explainable and predictable."

In the pharmacy profession, we are faced with a current rise in black swan events, namely loadshedding, cholera- and measles outbreaks, the recent looting in KZN, and lastly, litigation from the Independent Practitioners Association's Forums (IPAFs). The South African Pharmacy Council (SAPC) and the IPAF recently appeared in court (Tuesday, 23 May 2023) regarding an application to set aside Board Notice 101 of 2022. The matter pertains to the legislation the SAPC published in the Government Gazette in August 2021 to enable pharmacists to prescribe and dispense antiretroviral medicines/treatment (ART) for the treatment and prevention of HIV. The initiative, known as Pharmacist-Initiated Management of ART, or PIMART, aims to address the low rates of uptake of ART prophylactic treatment in South Africa and close the gap between the numbers of people diagnosed with HIV and those initiated onto treatment. The supplementary training for PIMART, guidelines and policies were developed between August 2018 and August 2021 (when legislation for PIMART's implementation was published). These were developed by the SAPC in close collaboration with the South African HIV Clinician's Society (SAHCS). Sadly, almost two years after the legislation was published, pharmacists remain unable to initiate ART in South Africa.

This despite the fact that the delayed diagnoses and treatment among youth are likely to lead to an increased risk of morbidity and increased onward transmission of the virus (horizontally and vertically). Less than two-thirds of people living with HIV were on ARVs in the months following the policy to put all those diagnosed with HIV on treatment. In South Africa, over 175 000 people acquired HIV in 2021, yet, less than 1% of sexually active individuals in the country were using pre-exposure prophylaxis (PrEP) to protect themselves from HIV in 2022.

A response to these concerns was drafted as a letter to the Minister of Health in October 2021 by a group of stakeholders consisting of heads of pharmacy schools and departments, pharmacy researchers, practitioners, and academics. The letter was published as a correspondence article addressed to the Editor of the South African Medical Journal (SAMJ) in December 2021.[1] The correspondence highlighted international trends, existing precedents for pharmacist-initiated therapy in South Africa and the additional extensive training that pharmacists must undergo. Following the recent court appearance on 23 May 2023, judgment is now expected to be handed down within three months of the date of the hearing.

In the face of these events, now more than ever, there is a heightened need for the pharmacy profession to check their readiness for these emergency situations. In the face of these "black swan" events, we need to embrace the unexpected, and consider new opportunities. This could include harnessing the experiences of pharmacists and pharmacist assistants who led and participated in recent unexpected events, including how they pivoted to manage them.

As a profession, we will never be able to predict the unpredictable, but we can be more resilient and lean into these challenges with a new way of thinking and vigour.

Happy reading, onwards and upwards!

Warm wishes,

Natalie

References

1. Moodley S, Gray A, Schellack N, et al. Pharmacist-initiated antiretroviral therapy (PIMART). S Afr Med J. 2021;111(12):1162-3. https://doi.org/10.7196/samj.2021.v111i12.16262.

President's Message

Work–life balance

Joggie Hattingh
PSSA President

Colleagues,

Over the years, I became aware that pharmacists as a group share a lot of similar personality traits. I guess it comes with the territory!

We serve patients and clients; we have to be agreeable and caring to be successful in our jobs. We also tend to put our own interests on the backburner, whilst we address other people's urgent health needs.

I thus thought it appropriate to start with a famous speech by Bryan Dyson delivered at the 172nd commencement of the Georgia Tech Institute, on 6 September 1996.

"Imagine life as a game in which you are juggling some five balls in the air. You name them work, family, health, friends, and spirit and you're keeping all of these in the air.

You will soon understand that 'work' is a rubber ball. If you drop it, it will bounce back. But the other four balls – family, health, friends and spirit – are made of glass. If you drop one of these, they will be irrevocably scuffed, marked, nicked, damaged or even shattered. They will never be the same. You must understand that and strive for balance in your life".

To me this speech was an eye-opener! It is so true and has so much to say about how and what we prioritise in our lives.

For most of us, our work and our profession are what define us as a person. Many pharmacists experience a real and severe personal crisis when they retire. The feeling of not being valuable anymore and of not being able to contribute to society, nor being recognised for our worth, is overwhelming. We tend to put too much emphasis on our work life! I'm not saying that it is okay to mess up at work big-time; I am saying that we have to consciously look for balance in our lives. Nobody will build any of us a monument when we are gone.

Yet our family's perception of who we are and what we contribute remains intact after we retire. Do we value our family's love and appreciation enough? How many of us spend enough time and energy during our early career to foster and cherish our relationships with our spouse, children and extended family? Opportunities to do so that are lost in early career phase can never be retrieved, it is literally water under the bridge. It is extremely difficult to put Humpty Dumpty back together again!

I recently stumbled across the old song "Cat's in the Cradle" by Harry Chapin. If you do not know the song, please google the lyrics or listen to the YouTube version at https://youtu.be/puJt66yOTBw. It is both so ironic and yet so true! It really underpins the message I try to convey.

I guess what I'm trying to bring home is the following: Arrive for work on time, give it your best shot while at work, and then leave on time! Give your family, faith, friends and health the time and attention they deserve, as a balanced life is what makes us truly happy and fulfilled. Even if you are single… or should I say, especially?

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- Kuraflo **3% Adult Spray** is for children over 12 years and adults and assist in pregnancy rhinitis, swelling from allergens or bacteria, post-nasal drip, congestion, and infection.
- Kuraflo **Nasal Rinse** can be mixed at either 1.5% or 3% and are safe for any age. Nasal rinsing is still one of the best methods for severe infections and alleviating congestion, as well as using it as a postop treatment for cleansing.

Mesh vs jet nebuliser

Nebulising has become much more common over the last couple of years. Especially since the outbreak of COVID-19, there has been a dramatic increase in nebuliser and nebulising solution demand.

Mesh nebulisers have become much more popular, and about 60% of clinical trials are done with mesh nebulisers compared to about 36% of trials done with jet nebulisers.

Jet nebulisers work with a compressor to turn liquid into a mist. They are much bulkier, generate loud noise, and need a plug point to operate, limiting portability. There is also more medication residual, and because of air circulation in the chamber, medication may be diluted towards the end of nebulisation.

Mesh nebulisers are virtually silent and have shorter treatment times since medication passes through a vibrating mesh membrane the first time and has no circulation in the medication chamber. This results in almost no residual and is, therefore, more effective.

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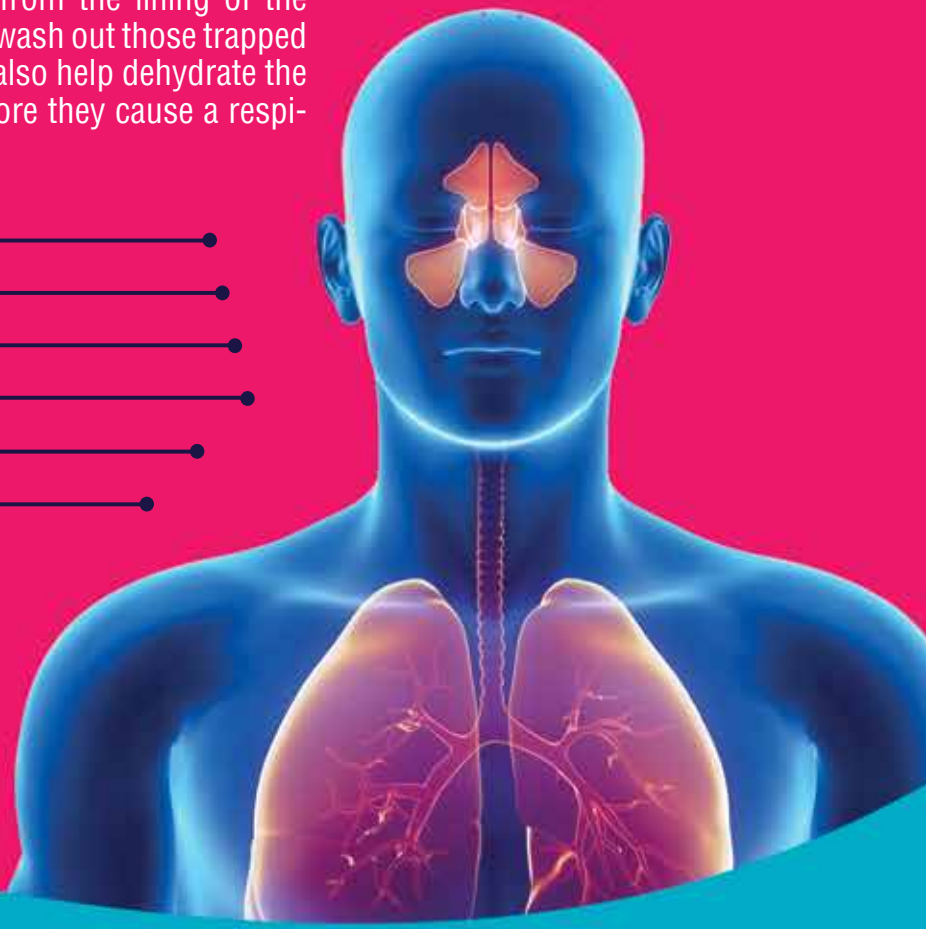

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Independent Community Pharmacy Association triumphs over Clicks

The below article was written for the SAPJ by ICPA's legal department

Introduction

The Independent Community Pharmacy Association (ICPA) is an organisation which provides independent community pharmacies with a collective strength and a coherent voice that is heard by government, medical schemes, pharmaceutical suppliers and importantly, the consumer.

ICPA represents one of the largest pools of professionals in the healthcare sector with over 1 200 pharmacies, about 3 000 pharmacists and 20 000 supportive healthcare personnel spread across metropolitan, urban and rural South Africa.

ICPA continues to have as its purpose the protection of the integrity of pharmacy and the providing of the best quality healthcare to patients and continues with this fight as is evidenced below.

Legal steps followed

On 6 May 2016, ICPA lodged a complaint against the Clicks Entities with the Department of Health, alleging a contravention of the Regulations on Ownership and Licencing of Pharmacies of 25 April 2003 ("**the Regulations**"). The Regulations were made under Section 49 of the Pharmacy Act 53 of 1974 ("**the Act**"). ICPA's complaint focused on the corporate group structure of the Clicks Entities and ICPA alleged that entities in the Clicks group have a beneficial interest in community pharmacies as well as a beneficial interest in a manufacturing pharmacy. Clicks Retailers (Pty) Ltd ("**Retailers**") operates the community pharmacies whilst the Unicorn Pharmaceuticals (Pty) Ltd ("**Unicorn**") is a manufacturing pharmacy.

Lawmakers in South Africa, and elsewhere in the world, have recognised that it is undesirable for the same person to have an interest in both a retailer and a manufacturer of medicines. This gives rise to a conflict of interest:

> *If a pharmacist stands to gain financially by promoting some medicines over others, consumers are exposed to the risk of not being provided with the best product or the lowest-priced product. There will also be a risk that medicines may be recommended and sold to consumers who do not need them.*
>
> *In addition, the conflict of interest may result in the manufacturer providing its products to "related" retail pharmacies only, i.e., those belonging to the same group of business entities as the manufacturer. This will prejudice pharmacies not belonging to the group and their customers. They will not have access to the group's medicines, as they are reserved for the group's own pharmacies and customers.*

It is therefore evident that the complaint was more centred on the patient's right than it was on the profit-generated model of Clicks.

The Minister of Health ("**the Minister**"), in an explanatory affidavit filed on the Minister's behalf, stated regarding the regulations that governed the dispute between ICPA and the Clicks Entities, that:

> *"The obvious purpose of the regulation was to ensure that pharmacists did not have a vested interest in the drugs they dispensed or recommended.*
>
> *Essentially, and in broad terms, what was proscribed was direct or indirect ownership of a community pharmacy where such pharmacy was vertically integrated with the holding of, or derivation of benefit from, a manufacturing licence.*
>
> *[The] objective is to ensure that when a pharmacy's pharmacist dispenses prescribed medicines or recommends them under certain circumstances, such pharmacy does not have a vested interest in the sale of such products. Such vested interest may arguably arise because of the ownership of, or beneficial interest in, a manufacturing pharmacy."*

Despite this intention, in a letter dated 19 January 2017, the National Department of Health ("**NDoH**") through Dr T Pillay rejected the complaint lodged by ICPA.

ICPA not being satisfied with the decision of the NDoH, lodged an appeal to the NDoH Appeal Committee against the Director-General's decision in terms of section 22(11) of the Act on

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*MAXALT RPD Wafer

REFERENCES: 1. Ferrari MD, Roon KI, Lipton RB, *et al.* Oral triptans (serotonin 5-HT$_{1B/1D}$ agonists) in acute migraine treatment: a meta-analysis of 53 trials. *Lancet.* 2001;358:1668-1675. **2.** MAXALT Approved Package Insert, March 2018. **3.** Mathew NT, Kailasam J, Meadors L. Early Treatment of Migraine with Rizatriptan: A Placebo-Controlled Study. Headache. 2004;44(7):669–673. **4.** Ahrens SP, Farmer MV, Williams DL, *et al.* Efficacy and safety of rizatriptan wafer for the acute treatment of migraine. *Cephalalgia.* 1999;19:525-30.

SELECTED SAFETY INFORMATION: CONTRA-INDICATIONS: Hypersensitivity to rizatriptan or any of the ingredients of MAXALT; concurrent administration of monoamine oxidase (MAO) inhibitors including linezolid, or use within 2 weeks of discontinuation of MAO inhibitor; in patients with uncontrolled hypertension; established coronary artery disease, including ischaemic heart, signs and symptoms of ischaemic heart disease, or Prinzmetal's angina; pregnancy and lactation; patients under 18 years of age; history of stroke or TIA; peripheral vascular disease, including (but not limited to) ischaemic bowel disease. **WARNINGS AND SPECIAL PRECAUTIONS:** Plasma concentrations of rizatriptan and its active N-monodesmethyl metabolite were increased by concomitant administration of a MAO-A inhibitor including linezolid. Only to be administered to patients in whom clear diagnosis of migraine has been established and not to be administered to patients with basilar or hemiplegic migraine. Not to be used to treat "atypical" headaches. Patients in whom CAD is established should not be given MAXALT. Other 5-HT$_{1B/1D}$ agonists (e.g. sumatriptan) should not be used concomitantly. Administration of ergotamine-type medications (e.g. ergotamine, dihydro-ergotamine or methysergide) and MAXALT within 6 hours of each other is not recommended. Cases of life-threatening serotonin syndrome have been reported during combined use of selective serotonin reuptake inhibitors (SSRIs)/serotonin norepinephrine reuptake inhibitors (SNRIs) and triptans. In adult patients receiving propranolol, the 5-mg dose should be used. **Use in the elderly:** The pharmacokinetics of rizatriptan were similar in elderly (aged ≥ 65 years) and in younger adults. Migraine or treatment with MAXALT may cause somnolence in some patients. Dizziness, ataxia, disorientation, blurred vision and vertigo have also been reported. MAXALT contains lactose. **SIDE EFFECTS: Adults:** The most common side effects reported in clinical studies were dizziness, somnolence and asthenia/fatigue. **Additional side effects reported in clinical studies include:** Common (≥1/100, <1/10): Paraesthesia, headache, hypoaesthesia, decreased mental acuity, tremor, palpitation, tachycardia, hot flushes/flashes, pharyngeal discomfort, dyspnoea, nausea, dry mouth, vomiting, diarrhoea, flushing, sweating, regional heaviness (pain, pressure, discomfort or a strange feeling/sensation in the back, neck, jaw, upper belly or in the shoulders or arms and pain in abdomen or chest.

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ZA-MXT-110017 03/25

17 February 2017. The appeal focused yet again on the structure of the Clicks Entities, and the complaint about that structure was summarised as follows:

> *"The purpose of Regulation 6 is precisely to prevent the same entity (Clicks Group and New Clicks) or person (said directors of Retailers) to hold beneficial interests in both community pharmacies and a manufacturing pharmacy so as to minimise the risk of the former promoting the medicines of the latter, which would not be in the patients' best interests and would contravene the entire structure of the Act. Financial interests should not be pitted against the best interests of patients [who] are entitled to be provided with the best product at the lowest price. Such a conflict of interest also imperils the patient's right to access to healthcare, entrenched in s 27 of the Constitution of the Republic of South Africa, 1996. It would also be arbitrary, and contrary to the rule of law, for the clear purpose of the statutory scheme to be circumvented through the adoption of a scheme such as the Click Group structure."*

After several months of delay, mainly caused by numerous procedural objections raised by Clicks regarding matters such as standing, non-joinder, separation of issues and appealability, the appeal hearing eventually took place on 29 November 2017. The appeal was dismissed by the Appeal Committee in a written decision handed down on 15 January 2018. The Appeal Committee dismissed all the procedural and technical objections raised by Clicks. It nevertheless rejected the appeal on the merits, i.e. it found that the Clicks' corporate structure did not violate the prohibitions contained in the Regulations.

On 29 June 2018, ICPA launched review proceedings in the Western Cape Division of the High Court aimed at setting aside the decisions of the Director-General and the Appeal Committee. This review application in the Western Cape High Court was successful and Judge Sievers found in ICPA's favour.

The Clicks Entities then sought and obtained leave to appeal to the Supreme Court of Appeal (SCA). Their appeal ultimately succeeded. This resulted in the High Court's order being set aside and ICPA's application being dismissed. ICPA once again unsatisfied with the decision against it, approached the Constitutional Court.

The legal background and court findings

1. Section 22A of the Act provides as follows:

   "22A Ownership of pharmacies

   The Minister may prescribe who may own a pharmacy, the conditions under which such person may own such pharmacy, and the conditions upon which such authority may be withdrawn."

2. Regulation 6(d) provides as follows:

   "6 Ownership of community pharmacies

   Any person may, subject to the provisions of regulation 7, own or have a beneficial interest in a community pharmacy in the Republic, on condition that such a person or in the case of a body corporate, the shareholder, director, trustee, beneficiary or member, as the case may be, of such body corporate–

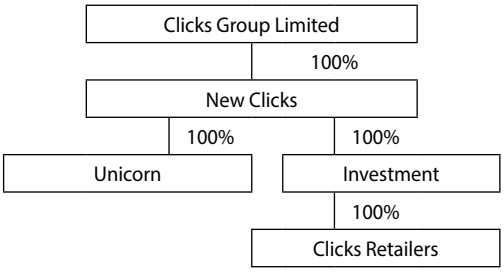
   (a) …

   (b) …

   (c) …

   (d) is not the owner or the holder of any direct or indirect beneficial interest in a manufacturing pharmacy."

It is common cause that Clicks is structured as schematically represented below:



The germane question was whether the Clicks Structure fell foul of Section 22A and Regulation 6(d). The interpretation of the term "beneficial interest" was central to answering this question.

Clicks argued since the assets of a company do not belong to the shareholders of the company but to the company itself, a shareholding in a company can never translate into a "*beneficial interest*" in the company's assets.

The Western Cape High Court, through Judge Sievers, found that a company holding 100% of the shares in another company does indeed have a beneficial interest in the subsidiary's assets, within the meaning of Regulation 6. It reasoned as follows:

> *"One must not only have regard to the text, but also to the context and purpose of Regulation 6(d). The context is that it is undesirable for there to be a direct or indirect beneficial interest in both a community pharmacy and a manufacturing pharmacy. An entity having interests in both types of pharmacies [retail and manufacturing] would gain financially if the manufacturing pharmacy's products are promoted by the pharmacists in community pharmacies over others. This could result in consumers not getting the best product at the best price".*

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

> *"the fact that the assets of a company do not belong to the shareholders does not necessarily mean that the shareholders do not have an interest in them. Of course they do."*

> *"Another danger is that if pharmacies are permitted to create their own affiliated manufacturers whom they control, directly or indirectly, they would directly be involved in setting prices and have strong incentives to keep those prices high. There is an inherent conflict of interest when a pharmacist is employed and remunerated by an entity which forms part of a group which*

also owns or has an interest in a manufacturing entity. The high court further pointed out, an entity having interests in both types of pharmacies would gain financially if the manufacturing pharmacy's products are promoted by the pharmacists in the community pharmacies over other products. This could result in consumers not getting the best quality product at the best price. Products which are not strictly needed might be recommended and sold. The conflict of interest could also result in the manufacturing pharmacy favouring community pharmacies belonging to the same group above outside or independent pharmacies. This might affect the availability of products to customers."

On 28 March 2023, the Constitutional Court through Justice Rogers finding in favour of ICPA, writing the judgment for the majority (5 judges to 4), stated that:

"The preference for a more generous interpretation is fortified by the Constitution. I have already mentioned the injunction in Section 39(2) of the Bill of Rights. Section 27(1) of the Bill of Rights guarantees to everyone, amongst other things, the right to have access to healthcare services. In terms of Section 27(2), the state must take reasonable legislative and other measures, within its available resources, to achieve the progressive realisation of this right. The dispensing of medicines by community pharmacies is an important part of health care services. An interpretation which promotes more effectively the best interests of the clients of the community pharmacists should be preferred over one which gives greater scope for perverse commercial incentives. There is nothing in the spirit, purport or objects of the Bill of Rights which pulls in the other direction."

Accordingly, the Constitutional Court set aside the SCA decision, upheld ICPA's appeal with legal costs and referred the question of sanctions against Clicks to the Director-General of the NDoH.

Conclusion

ICPA for years argued that a conflict of interest or temptation might exist within the Clicks Group as Clicks owns more than 600 pharmacies and also owns a manufacturing pharmacy, Unicorn Pharmaceuticals. The temptation for Clicks Pharmacies to actively promote their own brands at the possible expense of patient care was forefront in this argument. The Constitutional Court agrees with ICPA.

ICPA is morally mandated to keep on fighting for the best interest of pharmacy patients and will continue to lobby the necessary authorities to bring about an industry that remains driven by the desire to serve the communities wherein they trade. Pharmacy is not a business, it's a profession guided by an Ethical Code of Conduct, and it requires individuals with enduring qualities to remind the industry of the purpose which pharmacy serves. The purpose of healthcare and being the first point of call for ill patients, especially in these dire economic times.

ICPA will now be investigating their options in respect of the sanctions that the Director-General of Health may impose on Clicks. Whether that be the closing of Pharmacies, the revocation of the Unicorn's manufacturing licence or a fine, is too early to tell. On 28 March 2023, ICPA addressed a letter to the Director-General, and on 6 April 2023 their attorneys VanderSpuy Cape Town addressed a letter too, requesting that a moratorium be placed on the granting of all new licence applications to Clicks now that Clicks have been found to be in contravention of the act. ICPA awaits the Director-General's formal response. The continuing contravention of the Pharmacy Act and its regulations cannot be allowed and the NDoH will have to act swiftly against Clicks in this regard.

ICPA will further report this judgment to various other statutory bodies and request that they investigate other corporates who might indeed be falling foul of pharmacy legislation and regulations.

ICPA would like to recognise the sterling work of its legal team, VanderSpuy Cape Town led by Charles van Breda and Yaseen Carriem, and the Advocate Team of Jeremy Muller SC, Johan de Waal SC and Alfred Cockrell SC. Hard work and late nights have paid off and paved a new dawn for pharmacy.

The PSSA/Alpha Pharm distance learning programme 2023

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 2 – Irritable bowel syndrome

Irritable bowel syndrome (IBS) remains one of the most common gastrointestinal disorders seen by doctors in primary and secondary care. It is the most diagnosed gastrointestinal condition and is second only to the common cold as a cause of absence from work. While IBS is not a life-threatening condition, the disorder has a substantial impact on quality of life and social functioning.

IBS is characterised by chronic abdominal pain and altered bowel habits in the absence of any organic cause. IBS was for many years considered to be a functional gastrointestinal disorder, which implied that the patient experienced gastrointestinal symptoms in the absence of a specific cause or disease state. However, substantial advances have been made in understanding the complex pathophysiology of IBS, resulting in its re-classification as a **disorder of gut-brain interaction**, rather than a functional gastrointestinal disorder.

There has been a considerable amount of new evidence published concerning the diagnosis and management of IBS and both the British Society of Gastroenterology and the American College of Gastroenterology have updated their guidelines on the management of IBS.

Since many patients may have IBS-type symptoms for many years without consulting a doctor, often managing their symptoms with medicines available over-the-counter (OTC) in the pharmacy, the pharmacist can play an important role in identifying and assisting the patient with IBS. This module provides an update on IBS for the pharmacist and discusses the latest information on the causes, diagnosis, and management.

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 2023 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 2, 2023 – Constipation and diarrhoea in the pharmacy

Constipation is a common complaint and is often self-treated based on the patient's impression that there has been a change in normal bowel function. However, the term constipation may mean different things to different people.

Many people believe that a daily bowel movement is necessary for good health. Therefore, an important health role for the pharmacy front shop staff is to educate people about normal bowel function. It is, however, essential to find out from the person complaining about constipation, if their bowel habits have changed from what is usual for them. It may be necessary to refer people with persistent constipation to their doctor for further evaluation.

Diarrhoea is not a disease but can be a symptom of several illnesses. It is usually a symptom of an infection in the intestinal tract, which can be caused by various bacteria, viruses, or parasitic organisms. The infection is typically spread by the intake of contaminated food or water, or from person-to-person because of poor hygiene.

The most severe threat posed by diarrhoea is dehydration. During an episode of diarrhoea, water and electrolytes are lost through the frequent passing of liquid stools. Dehydration happens when these water and electrolyte losses are not replaced. Dehydration may rapidly progress from mild to moderate to severe, particularly in young children and the elderly.

This module discusses constipation and acute infectious diarrhoea (gastroenteritis) and their management in the community pharmacy setting.

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.

Celebrating small wins: a recap of the first quarter

"Quartely reflections create an opportunity to celebrate little wins." – *Anonymous*. Reflections are a great way of identifying and appreciating the good that has been accomplished and developing new ways to improve going forward. One of the functions of the YPG is to acquaint its members with the PSSA and promote its goals by encouraging active participation in the Society's projects and activities. As we close off the first quarter of the year, the YPG would like to reflect on this function and celebrate some of its achievements.

YPG at SAPHEX

The 2023 mentorship programme was successfully launched in February and is well underway with 10 mentorship pairs who are dedicated to sharing knowledge and experiences with the aim of growing the next generation of pharmacy leaders in the Society and the profession as a whole.

Many young pharmacists attended and contributed to the Annual General Meetings, conferences and National Executive Commmittee meetings of various branches of the PSSA, SAACP and SAAHIP. The SAPHEX symposium was one of the highlights for the YPG as it played a supportive role to the PSSA by assisting with the stand presentations, session chairing and facilitating networking amongst young pharmacists. The YPG also delivered presentations during the pharmacist internship and community service pharmacist inductions in the Cape Western Province branch.

The YPG used social media as a tool to highlight a wide range of health awareness days including World Cancer Day (4 February), National STI/Condom Awareness Week (12–16 February), World Obesity Day (4 March) and World Tuberculosis Day (24 March). The YPG also created educational infographics with the aim of spreading awareness of the measles and cholera outbreaks nationwide. It goes without saying that the YPG could have achieved a lot more during the first quarter, however, as we step into the second quarter of the year we choose to reflect on and celebrate the things we have achieved and hope to continue to bring more young people pursuing the profession of pharmacy, towards the Society who will ultimately make positive contributions to its growth and the profession at large.

"Win small, win early, win often" – Gary Hamel *Author of Leading the Revolution: How to Thrive in Turbulent Times by Making Innovation a Way of Life.*

Young pharmacists at the SAAHIP 2023 conference

A reflection by Alexander Wehmeyer (YPG PRO 21/22)

The 2021/2022 YPG Steering Committee had the superb opportunity to attend the 2023 SAAHIP Conference that was held from 9 to 11 March at the Champagne Sports Resort in the picturesque Drakensberg. The experience can be best described as educational, inspiring and fun-filled with insightful academic presentations and exciting themed evening events.

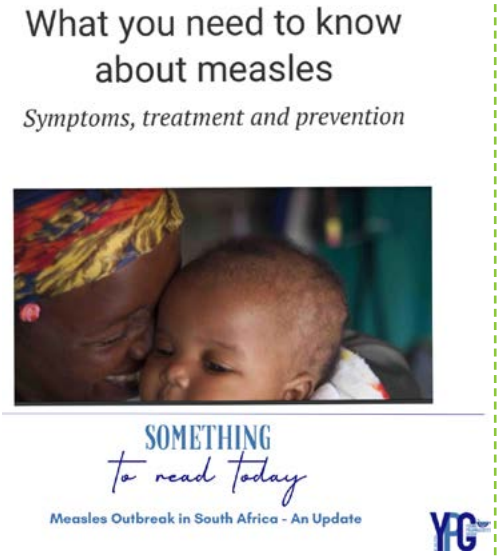
In addition to the annual YPG podium presentation at the conference, the team also hosted a light-hearted selfie competition, where young pharmacists in attendance were tasked with seeking out and taking selfies with the previous YPG steering committee. They were then asked to post the photos on social media and to tag the YPG page.

Congratulations are in order for Daniel Ramatsoma, who won the YPG selfie competition and received a great Takealot voucher as the prize.

YPG at the SAAHIP conference

What is happening on social media?

The YPG's social media pages are exciting platforms with over 600 young pharmacists who are keen on contributing to the growth of and becoming active participants of the Society and the profession. Each week, the YPG creates engaging posts ranging from motivational quotes, to news-worthy pharma articles, to Society member benefits, updates in legislation, pharmacy humour, and a crowd favourite, young pharmacists' feature. We encourage you to visit our pages for some interesting visual highlights of conferences and symposiums and to interact with us! See below for our social media handles, please like, follow and share our information.



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

Assessing the effectiveness of pharmacist-initiated strategies on prescription errors and drug-associated problems among geriatric patients within a hospital setting: a systematic review

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Abstract

Background: Geriatrics are a unique subgroup of patients, usually subjected to multiple medications and inappropriate prescribing, complicated by comorbidities. This study sought to assess if pharmacist-initiated strategies can reduce drug-related problems (DRPs) among the elderly in hospitals, either as outpatients or hospitalised patients.

Methods: A systematic review was carried out which included 11 peer-reviewed articles to assess if pharmacist-led strategies lower DRPs. Only interventional study articles in English published between 2017 and 2022, and free text searched from Google Scholar and PubMed were part of the study. The risk of bias was examined using the Cochrane risk of bias tool.

Results: Eleven studies were included summing up to 9 016 patients. Most studies reported a decrease in DRPs and improved quality of life following pharmacist interventions. However, drug-associated hospitalisation was not affected by the interventions. The acceptance rate was high (median = 80%).

Conclusion: Pharmacist interventions improve the quality of prescribing, reduce DRPs and enhance the quality of life but have no impact on hospital admissions whether or not they are drug-related. Pharmacist interventions are more effective if carried out in a multidisciplinary setting.

Keywords: prescribing error, geriatric, drug-related problems, pharmacist interventions, randomised controlled trial and interventional study

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Read the full article online at http://www.sapj.co.za/

Common deficiencies witnessed in Module 1 assessed by the pharmaceutical evaluation and management pre-registration unit within the South African Health Products Regulatory Authority

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Abstract

Background: Well-functioning health systems need effective medicine regulation. The regulatory authorities are governed by basic principles such as transparency, accountability and science to facilitate access to medicines. The South African authority has had a backlog for 10 years, delaying patient access to medicines. To increase transparency, a series of articles on common deficiencies were published. The sharing of deficiencies would assist applicants in improving their submissions in the regional, active pharmaceutical ingredient (API), finished pharmaceutical product (FPP) and bioequivalence sections. The current study focuses on the authority's common deficiencies in the regional section.

Methods: Module 1 deficiencies from sections evaluated by the pharmaceutical evaluation and management (PEM) pre-registration unit were collected from 2011–2017 applications. From 3 148 finalised applications, 325 non-sterile and 244 sterile were selected. A further analysis of 62 applications was evaluated between January and May 2021 to confirm the consistency of assessments and requirements.

Results: For the 2011–2017 study, 3 042 deficiencies were collected. Labelling sections accounted for 52% of the deficiencies, followed by amendment schedule (12%), general deficiencies (11%), foreign registration status section (10%), application details (8%) and good manufacturing practice (GMP) standards (7%). Labelling had the highest deficiencies (57%) in the 2021 study, followed by foreign regulatory status (15%) as well as GMP documentation and application details (10%). These deficiencies were found in 52 query letters, as 10 contained no queries from Module 1.

Conclusion: The qualitative and quantitative data provided herein intends to assist applicants in building quality submissions in order to convey acceptable regional requirements during submission, and reduce the authority›s overall registration turnaround time.

Keywords: regional section, Module 1, common deficiencies, SAHPRA

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Migraine: an evidence-based approach

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Abstract

Migraine is a common disabling primary headache disorder. Migraine management approaches include treatment of the acute attack and, depending on severity and frequency, providing agents to prevent further episodes. This brief review outlines the salient points of migraine management.

Keywords: migraine, headache, prodrome, aura, prophylaxis

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Introduction

Headache disorders are classified by the ICHD-III[1] as primary headache disorders, which include migraine, tension-type headache, cluster headache and other trigeminal autonomic cephalalgias, as well as other primary headache disorders, and secondary headache disorders which include a new headache occurring with another lesion capable of causing it (e.g., headache attributed to intracranial tumour). Migraine is a syndrome characterised by periodic headaches with complete resolution between attacks. The frequency of attacks is variable, occurring as low as several per lifetime to as high as several per week. Headache frequency may predict progression from episodic to chronic migraine.[2]

An attack may be composed of the following sequential stages: prodrome, aura, headache and resolution. A prodrome is a vague change in mood or appetite, while an aura is a clear neurological symptom such as a visual (flickering lights, spots or lines, and/or partial loss of vision), motor (speech) or sensory (numbness and/or pins and needles) disturbance. The moderate to severe pulsating pain may be uni- or bilateral, lasting up to 72 hours. In children, migraine is a diagnosis of exclusion.[3]

Migraine is the second most prevalent neurological disorder (after tension-type headache), with a female-to-male ratio of 3:1 and an estimated one-year prevalence of approximately 15% in the general population.[4] The prevalence peaks between the ages of 35 and 39 years, and about 75% of affected persons report the onset of migraine before the age of 35 years.[4] Since the disorder tends to remit with older age, onset of migraine after the age of 50 years should arouse suspicion of a secondary headache disorder.[4]

Acute treatment

The evidence-based National Institute for Health and Care Excellence (NICE) guidelines[5] suggest that for the acute treatment of migraine, combination therapy of an oral triptan (sumatriptan, zolmitriptan, rizatriptan, naratriptan or eletriptan) with either an NSAID (e.g. naproxen or ibuprofen), or with paracetamol, should be offered, taking the person's preference, comorbidities and risk of adverse events into account. These are best taken early in the attack when absorption may be least inhibited by gastric stasis. For people in whom oral preparations for the acute treatment of migraine are ineffective or not tolerated, a non-oral preparation of metoclopramide or prochlorperazine should be considered. An antiemetic such as metoclopramide or domperidone not only relieves the nausea that accompanies many migraine attacks but also enhances the efficacy of simultaneously administered oral analgesics.[7] Adding a non-oral NSAID or triptan if these have not been tried, should also be considered. Codeine or dihydrocodeine, which are used extensively in OTC combination analgesics[6] should not be used as they provide small additional benefit in a range of painful conditions, but evidence of this does not extend to headache and it is at the expense of increased side effects. In addition, these opioids are frequently implicated in medication overuse headache.

Prophylactic management of migraine with or without aura

Identifying and avoiding trigger factors can reduce the frequency of migraine attacks by up to 50%. It is often of value to ask the patient to keep a migraine diary recording frequency, duration and severity of attacks and to use this to monitor how effective headache interventions are. Only migraine recurring four or more times per month should be treated prophylactically.[7] It is important to review the need for continuing migraine prophylaxis six months after the start of preventative treatment.

Topiramate or propranolol

Topiramate (target dose 100 mg twice a day) or propranolol (target dose 60 mg once or twice a day) are the NICE-recommended first-line agents for the prophylaxis of migraine and these agents should be offered after a full discussion of the benefits and risks of each.[5] Topiramate should be started at a low dose (25 mg a day), and the dose should be increased over a period of two to three weeks to minimise side effects which may include cognitive slowing with perceived memory deficits and word-finding difficulties.

The risk of reduced effectiveness of hormonal contraceptives with topiramate, and the risk of foetal malformations with its use **must** be explained to your female patients. The importance of effective contraception (e.g. medroxyprogesterone acetate depot injection, an intrauterine method or combined hormonal contraception with a barrier method) for women and girls of childbearing potential who are taking topiramate should be emphasised. People with depression and migraine could be at an increased risk of worsening depression/anxiety with topiramate – in these cases, I find it beneficial to either start a concomitant antidepressant agent (usually an SSRI will suffice), or to use an alternative like valproate (300–1 000 mg BD)/pregabalin (25–75 mg BD), with the same safety/side effect information applying as above. Valproate may be limited by its somnolence, weight gain, hair loss, and possible hepatotoxicity and thrombocytopenia.

Amitriptyline

Amitriptyline is also an option for the prophylactic treatment of migraine according to the person's preference, comorbidities and risk of adverse events. I do find this less effective than the above, but it is a good starting point, and often addresses the tension-type component that accompanies migraines. Amitriptyline 10–150 mg daily, at or one to two hours before bedtime, is first-line when migraine co-exists with troublesome tension-type headache, another chronic pain condition, disturbed sleep or depression.[8] With the exception of the depressed patient, it is wise to explain the choice of this drug to patients who do not consider themselves depressed or they may reject it. Commonly reported adverse events include dry mouth, sedation, dizziness and nausea. These are most apparent in the first couple of weeks and usually settle with continued use.

Gabapentin should **not** be offered for the prophylactic treatment of migraine.

Migraine prophylaxis with botulinum toxin[9]

If topiramate, valproate, trepiline, pregabalin and propranolol are unsuitable or ineffective, consider referral to a specialist for Botox (155 units subcutaneously), but this is often limited by cost.

Botulinum toxin type A is recommended as an option for the prophylaxis of headaches in adults with chronic migraine (defined as headaches on at least 15 days per month of which at least eight days are with migraine) that has not responded to at least three prior pharmacological prophylaxis therapies and whose condition is appropriately managed for medication overuse.

CGRP monoclonal antibodies

Monoclonal antibodies to the calcitonin gene-related peptide (CGRP) pathway or its receptor may reduce disability even on non-headache days,[1] and may be useful treatment options in the future.[10] To include Aimovig is a promising new treatment for migraine that is available in South Africa. It is well tolerated with a good safety profile.

Conclusion

Migraine management can often be tricky, particularly as it often co-exists with other pathologies, and it is useful to approach the patient not only from a medication aspect, but to also discuss the non-medical supporting therapies, such as triggers, physiotherapy, keeping a headache diary, management of stress and anxiety and the like. With the advent of the CGRP monoclonal antibodies, available in SA, it is likely that migraine management will see a shift from the current therapies to these more targeted therapies.

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Clinical considerations for rational use of oral anticoagulant therapy

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Abstract

Patients who are at risk for venous thromboembolism may require prophylaxis with oral anticoagulant agents. In South Africa, available oral anticoagulant agents include warfarin and the new oral anticoagulants (NOACs): dabigatran, rivaroxaban and apixaban. Whilst NOAC agents have benefits over warfarin therapy in terms of therapeutic window, onset of action and monitoring requirements, multiple clinical factors need to be considered when selecting an anticoagulant agent for a patient.

This review article explores clinical considerations for the rational use of oral anticoagulants and includes discussions on bleeding events, risk of drug interactions, safety in renal and hepatic impairment, and safety and efficacy in obesity.

Warfarin and NOACs are subject to potential drug-drug interactions. It is important to consider the patient's concomitant medication and the clinical significance of interactions.

The safety of NOACs in kidney and liver disease has not been extensively explored; thus, the use of NOACs is often limited to patients with mild-moderate cases of these diseases. In more severe cases of disease, warfarin remains the drug of choice, subject to close international normalised ratio (INR) monitoring.

The safety of NOACs in obesity has not been adequately investigated. Further studies are required to inform anticoagulant recommendations in obese patients. In severely obese patients, warfarin, with close INR monitoring, remains the drug of choice.

When comparing warfarin and the NOACs, it is evident that there is no "ideal" agent which is preferable in all clinical settings. Rational use of anticoagulant therapy requires consideration of patient-specific factors. The information provided in this review aims to guide pharmacists when assessing the rational use of anticoagulant therapy.

Keywords: anticoagulant, venous thromboembolism, new oral anticoagulants

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Introduction

This review article will explore clinical considerations for the rational use of oral anticoagulants and will include discussions on managing bleeding events, risk for drug interactions, safety in renal and hepatic impairment, and safety and efficacy in obesity.

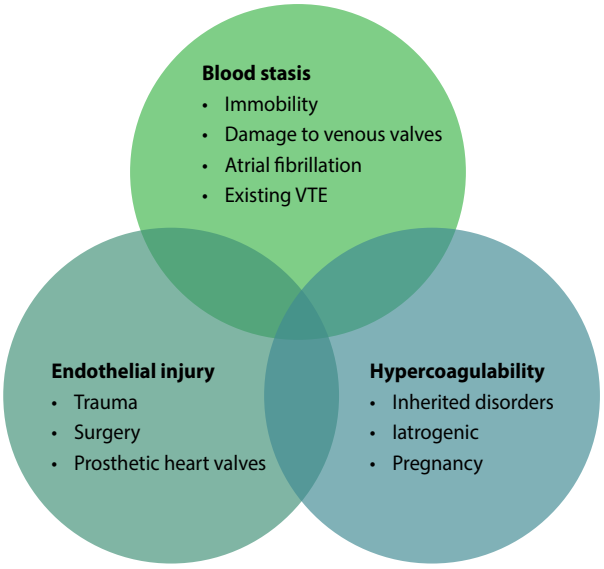


Figure 1: Virchow's triad of risk factors contributing to thrombus formation. Adapted from Witt et al.[3]

The information provided in this review aims to guide pharmacists when assessing the rational use of anticoagulant therapy.

An anticoagulant is a type of antithrombotic agent which interferes with the conversion of fibrinogen to fibrin.[1] Anticoagulant therapy can be delivered orally or parenterally and is indicated for prophylaxis and treating venous thromboembolism (VTE).[2] Risk factors for developing VTE can be classified according to Virchow's triad (Figure 1).[3] Patients at high risk of VTE may receive prophylactic anticoagulants for prolonged periods.[2] Where long-term anticoagulant therapy is indicated, oral agents are generally preferred over parenteral agents.[4]

In South Africa, available oral anticoagulant agents include warfarin (a coumarin anticoagulant) and the new oral anticoagulants (NOACs), which include: rivaroxaban, dabigatran and apixaban.[5] Table I summarises a few important characteristics of the oral anticoagulant options available in South Africa. The only oral anticoagulant available in the public healthcare sector is warfarin, whereas the private healthcare sector has access to warfarin and three NOAC options.[5,6]

Coumarin anticoagulants

Warfarin is the only coumarin anticoagulant registered in South Africa.[5] Warfarin is a vitamin K antagonist and thus achieves an

Table I: Oral anticoagulant agents available in South Africa

Active ingredient	Registered trade names in South Africa[5]	Mode of action[6]	Registered indications in South Africa[5]
Warfarin	Cipla Warfarin® Aspen Warfarin®	Vitamin K antagonist	Transient ischaemic attacks, thromboembolic disorders
Rivaroxaban	Xarelto® iXarola ® Rezalto®	Factor Xa inhibitor	Prevention of stroke and systemic embolism in patients with atrial fibrillation; treatment of acute and prevention of recurrent deep vein thrombosis (DVT) and pulmonary embolism (PE); DVT prevention following major orthopaedic surgery of the lower limbs
Dabigatran	Pradaxa®	Direct thrombin inhibitor	Prevention of stroke and systemic embolism in patients with atrial fibrillation; Treatment of acute and prevention of recurrent DVT and PE; prevention of VTE in patients who have undergone hip and knee replacement surgery
Apixaban	Eliquis® Zyquis®	Direct factor Xa inhibitor	Prevention of VTE in adults who have undergone hip or knee replacement surgery; prevention of stroke or systemic embolism in patients with atrial fibrillation

anticoagulant effect by inhibiting the function of the vitamin K epoxide reductase (VKOR) enzyme in the liver, which is normally responsible for converting vitamin K epoxide to reduced vitamin K. This reduced form of vitamin K (hydroquinone) is a key co-factor required for the carboxylation of clotting factors II, VII, IX and X, and natural anticoagulants proteins C and S.[1,7] Interference with carboxylation results in the formation of biologically inactive clotting factors.[7]

Warfarin has no effect on already synthesised clotting factors; thus, the onset of the anticoagulant effect may be delayed in accordance with the half-life of circulating clotting factors.[7] Aside from the delay in the onset of anticoagulation, the short half-life of protein C, an endogenous anticoagulant, means that serum levels of protein C drop rapidly and thus degrade prior to degradation of many circulating clotting factors. This may result in an initial paradoxical hypercoagulable state when initiating warfarin therapy. Thus, patients who are in an acute hypercoagulable state (for example, patients with an active VTE) require "bridging therapy" when starting warfarin. Bridging therapy involves co-administration with a heparin or low-molecular-weight heparin (LMWH) for approximately 5–7 days.[7]

The safety of warfarin depends on that therapeutic concentrations are maintained within a narrow therapeutic window. The therapeutic effect is monitored clinically using the international normalised ratio (INR). This is a useful tool for dosing adjustments but necessitates frequent laboratory testing, which may affect patient adherence.[8]

Warfarin is familiar to most prescribers and remains the most commonly prescribed oral anticoagulant agent worldwide.[9] The development of NOACs, also known as direct oral anticoagulant agents (DOACs), provides alternative options to warfarin. It is important that prescribers and pharmacists are aware of the benefits of NOAC agents while remaining mindful of the limitations and interactions associated with these agents.[8-10]

New oral anticoagulants

Rivaroxaban and apixaban function as direct factor Xa inhibitors in the final common pathway in the coagulation cascade.[1,7] Rivaroxaban and apixaban function directly on factor Xa (both free and clot-bound) and do not rely on antithrombin activity for their effect (Figure 2).[3]

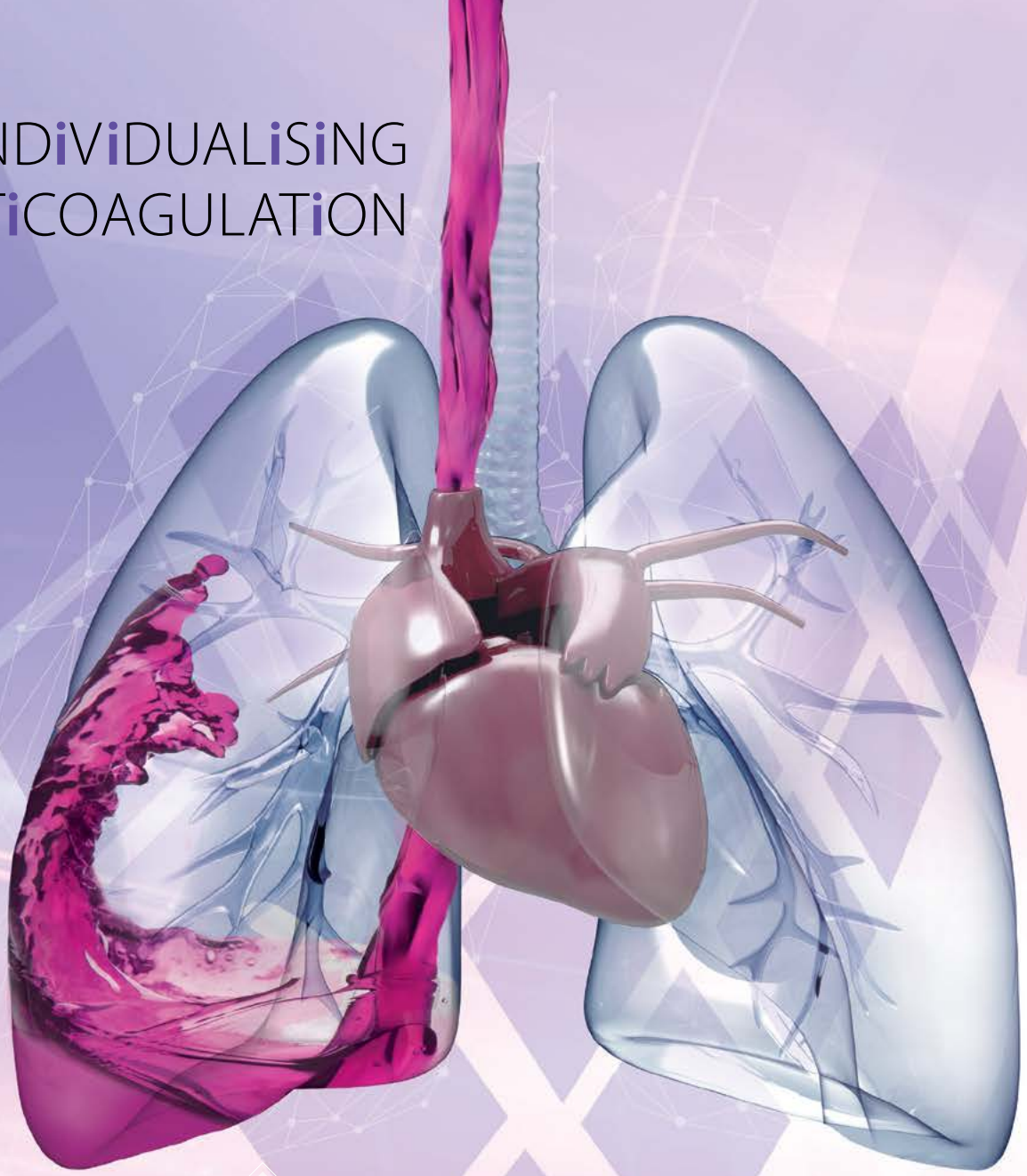
Fixed dosing regimens are recommended by the manufacturer for rivaroxaban and apixaban, depending on the indication. The onset of action of these drugs is rapid (peak response 2–4 hours after a rivaroxaban dose and 1–3 hours after an apixaban dose)[1,11] and does not require bridging therapy with injectable anticoagulants. Although monitoring of their effect is rarely required clinically, it can be accomplished using anti-Xa assays calibrated for the specific agent being used.[7]

Dabigatran etexilate is a prodrug which undergoes in vivo bioactivation to dabigatran, and is the only orally active direct thrombin inhibitor (Figure 2).[1] Bioactivation involves hydrolysis catalysed by plasma and hepatic esterase enzymes.[1] Fixed-dose regimens are also recommended by the manufacturer for dabigatran dosing, depending on the indication. The onset of action is rapid (2 hours), and provides a predictable anticoagulant response, which does not necessitate coagulation monitoring.[1]

The "ideal" anticoagulant

An ideal anticoagulant would prevent the development of pathological thrombi, whilst still allowing for the normal haemostatic response to endothelial injury without an increased risk of bleeding.[7] Other factors which may affect the desirability of an anticoagulant agent include predictable anticoagulant effect, available routes of administration (i.e. oral route preferred), adverse effect profiles, predictable pharmacokinetic profiles, less frequent dosing, the risk for drug-drug interactions, availability of a reversal agent and a broad therapeutic window.[10,12] Although NOACs possess desirable characteristics in terms of a wide therapeutic window and predictable pharmacokinetics, there are some concerns about the lack of availability of reversal agents. It

iNDiViDUALiSiNG ANTiCOAGULATiON



Treatment of pulmonary embolism (PE*) and for the prevention of recurrent pulmonary embolism (PE*) [1]

S4 iXarola®

Rivaroxaban

A Xarelto® clone

sanofi

*PE - PULMONARY EMBOLISM

Other indications of the iXarola® product range:

iXarola® 10 film-coated tablets are indicated for: Prevention of venous thromboembolism (VTE) in patients undergoing major orthopaedic surgery of the lower limbs. Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

iXarola® 15 and iXarola® 20 are indicated for: Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation. Treatment of deep vein thrombosis (DVT) and for the prevention of recurrent deep vein thrombosis (DVT) and pulmonary embolism (PE). Treatment of pulmonary embolism (PE) and for the prevention of recurrent pulmonary embolism (PE) and deep vein thrombosis (DVT).

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. Floor 5, Building 1, Hertford Office Park, 90 Bekker Road, Midrand, 2196. Reg. No. 1996/10381/07. For medical information enquiries kindly contact ZA.Medinfo@sanofi.com. Tel: (011) 256 3700.

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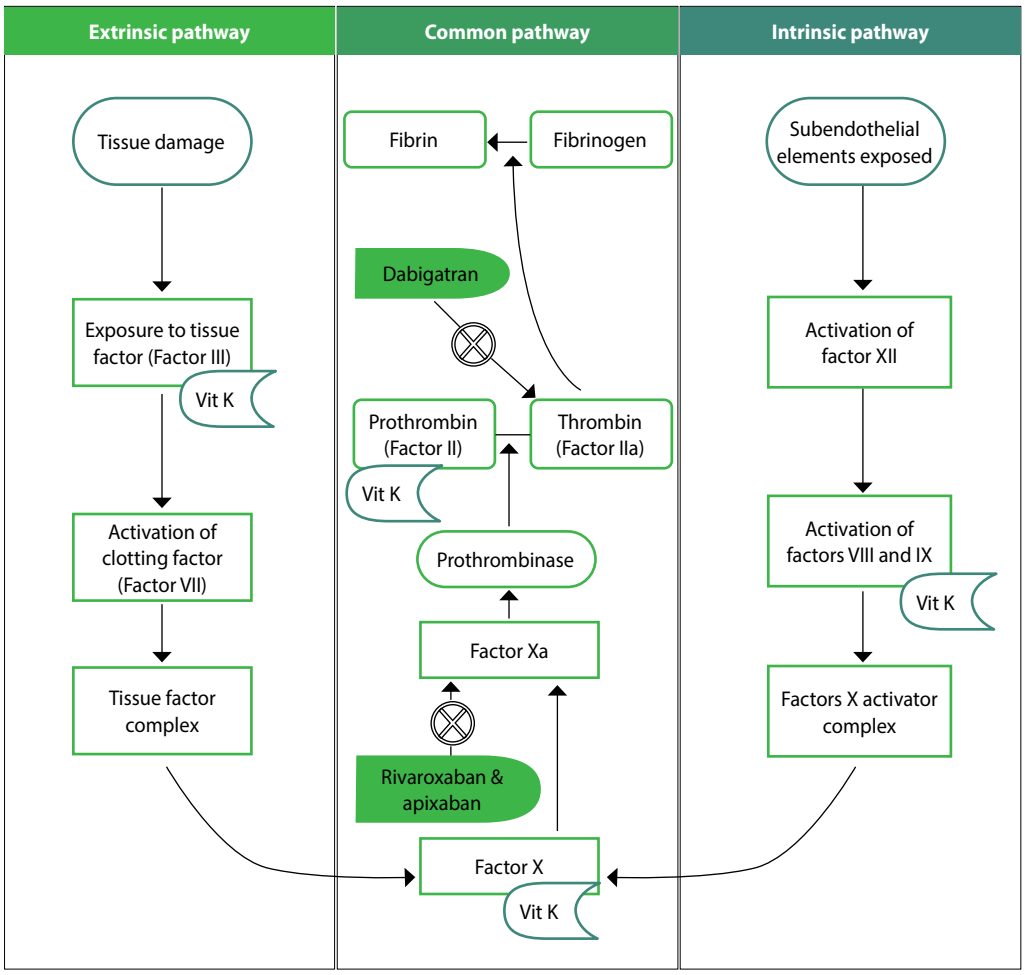

Figure 2: Coagulation cascade and sites of action of NOACs

could be argued that there is no "ideal" anticoagulant, and that anticoagulant selection should be individualised to the patient's needs.

Clinical considerations

Bleeding events

The most concerning adverse effect associated with warfarin and NOACs is bleeding. The risk for intracranial bleeding is greater with warfarin use compared to NOAC agents (50% lower risk with rivaroxaban and apixaban, and a 70% lower risk with dabigatran).[1,13-15] The risk for gastrointestinal tract bleeding is higher for rivaroxaban and dabigatran than warfarin.[1,13-15] Overall, severe bleeding events occur less frequently with NOAC agents since NOAC agents have shorter half-lives than warfarin.[16]

Guidelines for managing bleeding in warfarin toxicity are well established, involving interruption of warfarin therapy, administration of an antidote (phytomenadione or vitamin K_1), and/or administration of blood products like fresh frozen plasma. The exact treatment approach is dependent on the INR and severity of the bleeding.[6]

The management of bleeding events in patients receiving NOAC therapy involves gastrointestinal decontamination by activated charcoal (within 2 hours of ingestion of rivaroxaban or apixaban and within 4 hours of ingestion of dabigatran), investigating the source of bleeding, supportive care and rehydration.[16] Additional measures for major bleeding include haemodialysis (for dabigatran) and adjunctive therapies, such as antifibrinolytic therapy or transfusion of blood products (for all NOACs).[17] A specific antidote for the reversal of dabigatran effects, idarucizumab (Praxbind®) is now registered in South Africa for emergency surgical procedures or life-threatening bleeds in patients treated with dabigatran.[5]

Drug interactions

Drug interactions form an important component of anticoagulant stewardship reviews since interactions have the potential to impact the efficacy and safety of the anticoagulant agent.[16] There are two main categories of drug interactions which need to be considered: pharmacokinetic and pharmacodynamic interactions.[9,19] Pharmacokinetic interactions involve alterations in the absorption, distribution, metabolism or elimination of the affected agent. Pharmacodynamic interactions occur when the interacting drugs have additive or opposing pharmacological or physiological effects.[19] Table II provides examples of clinically significant pharmacokinetic and pharmacodynamic drug interactions between oral anticoagulants and other medications.

Table II: Summary of clinically relevant drug interactions with oral anticoagulants

Oral anticoagulant	Interacting medication	Mechanism of interaction	Effect on anticoagulant activity	Recommendation
Pharmacodynamic interactions				
Warfarin, dabigatran, rivaroxaban, apixaban	Mirtazapine, venlafaxine, desvenlafaxine, fluvoxamine, citalopram, sertraline, escitalopram,	Serotonergic agents increase the risk of bleeding when co-administered with oral anticoagulants[11]	Enhanced	Monitor INR if co-administering warfarin with serotonergic agents Monitor for signs of bleeding and discontinue if pathological bleeding occurs[11]
	Aspirin, clopidogrel, prasugrel, dipyridamole, eptifibatide	Additive effects with antithrombotic agents[11]	Enhanced	Monitor for signs of bleeding. Only combine when clinically indicated[11]
Pharmacokinetic interactions				
Warfarin	Cholestyramine, sucralfate	Decrease in absorption and possible enterohepatic recycling of warfarin[6,11]	Diminished	Take cholestyramine 3–6 hours after a dose of warfarin[6,11] Take sucralfate at least 2 hours apart from warfarin dose[6,9]
	Ciprofloxacin, fluconazole, voriconazole, propranolol	Inhibition of CYP1A2-mediated metabolism of warfarin.[9,11]	Enhanced	Avoid combination; if indicated, monitor INR closely, especially when starting and stopping the CYP450 inhibitor[11]
	Fluconazole, voriconazole, amiodarone, atorvastatin, quinidine, diltiazem, lovastatin, simvastatin, telmisartan	Inhibition of CYP3A4-mediated metabolism of warfarin[9,11]	Enhanced	Monitor INR closely, and adjust the dose accordingly Dose reduction with amiodarone may be required[6,9,11]
Dabigatran	Verapamil, amiodarone, ketoconazole	Strong P-glycoprotein efflux pump inhibitors increase exposure to dabigatran[9,11]	Enhanced	Avoid combination; decrease dose of dabigatran if combined with verapamil/ amiodarone[6,9,11]
	Clarithromycin, quinidine, azithromycin, erythromycin	Moderate P-glycoprotein efflux pump inhibitors may increase exposure to dabigatran[9]	Enhanced	Use with caution; ensure a two-hour dose spacing interval;[9] avoid combination in patients predisposed to increased dabigatran exposure (renal impairment and elderly)[9,11]
	Rifampicin, phenytoin, St John's wort, carbamazepine	P-glycoprotein efflux pump inducers may decrease exposure to dabigatran[9,11]	Diminished	Avoid combination[11]
Apixaban	Ketoconazole	Strong P-glycoprotein efflux pump inhibitor and CYP3A4 inhibitors increase apixaban exposure[9,11]	Enhanced	Avoid combination; if necessary, decrease apixaban dose by 50% during co-administration[9,11]
Rivaroxaban & apixaban	Rifampicin, phenytoin, carbamazepine, phenobarbital, St John's wort	CYP3A4 induction leads to decreased exposure to rivaroxaban and apixaban[9,11]	Diminished	Avoid combination[11]
Rivaroxaban	Ketoconazole, ritonavir	CYP3A4 and P-glycoprotein inhibition leads to increased exposure to rivaroxaban[9,11]	Enhanced	Avoid combination[11]

Absorption-related drug interactions

Mechanisms of absorption-related drug interactions may involve chelation, alterations in gastric pH, alterations in P-glycoprotein transporter function or alterations in first-pass metabolism.[20] Warfarin, dabigatran and apixaban are oral anticoagulants that are implicated in absorption-related interactions.

Although the bioavailability of warfarin is high, absorption of warfarin is reduced when co-administered with cholestyramine or sucralfate due to chelation interactions.[9] Therefore, doses of warfarin and cholestyramine should be spaced by 3–6 hours, whereas doses of warfarin and sucralfate should be spaced by 2 hours.[6]

Dabigatran has a poor bioavailability (6–7%), primarily because it is a P-glycoprotein efflux transporter substrate. It also relies on acidic conditions for solubility and absorption, which means that co-administration with drugs like proton pump inhibitors could further reduce absorption and bioavailability of dabigatran.[21] To optimise bioavailability, tartaric acid is incorporated into the dabigatran etexilate capsules.[22,23] The inclusion of tartaric acid in dabigatran formulation limits the significance of interactions reported from co-administration with proton pump inhibitors.[21]

On the other hand, co-administration with potent P-glycoprotein inhibitors, such as verapamil and amiodarone, may increase the bioavailability of dabigatran and predispose the patient to dose-dependent adverse effects.[6,21] To mitigate this, doses of dabigatran should be reduced when co-administered with verapamil or

amiodarone.[9] Dose adjustments are not required with other P-glycoprotein inhibitors. However, the recommendation is to ensure a 2-hour dose spacing interval between P-glycoprotein inhibitors and dabigatran.

The bioavailability of apixaban is limited (50%) due to the activity of P-glycoprotein and breast cancer resistance protein (BCRP) efflux mechanisms.[21] Drugs affecting only the absorption of apixaban are rarely clinically significant. The clinical significance of interactions with apixaban is greater when multiple mechanisms of interactions occur concurrently. For example, apixaban interacts with ketoconazole since ketoconazole inhibits P-glycoprotein and BCRP-mediated gastrointestinal efflux transporters. Ketoconazole also inhibits the CYP3A4-mediated metabolism of apixaban (CYP3A4 contributes to 15% of apixaban clearance).[21] The combined effect of these multiple drug interaction mechanisms increases apixaban exposure.[21]

Distribution-related drug interactions

Mechanisms for distribution-related drug interactions include plasma protein displacement interactions, displacement from target binding sites and interference with tissue barriers through alteration of P-glycoprotein transporter activity.[20] In terms of anticoagulant interactions, the primary distribution-related interactions involve plasma protein binding displacement interactions with warfarin. Distribution-related interactions involving NOACs are not well documented, with more interactions focused on the absorption and metabolism of NOACs.

Warfarin is highly plasma protein bound (99%) and is thus subject to plasma protein binding displacement interactions with highly plasma protein-bound drugs, such as ibuprofen, quinidine, amlodipine, losartan and fenofibrate.[6,9] The displacement of warfarin from plasma protein binding sites is associated with transient and marginal increases in prothrombin time test (PT) and the international normalised ratio (INR).[9] The onset of this effect is generally delayed and can occur within one day to three weeks of starting the interacting drug.[9]

The clinical significance of protein displacement interactions has been disputed.[20,25-32] Since plasma protein displacement interactions increase the free (unbound) concentration of the drug, it is expected that an increase in effect would be observed. However, the increase in effect would be limited and transient since the increased unbound concentration of the drug will also increase the clearance of the drug.[20,33] Furthermore, in the case of warfarin, the clinical significance of the transient effect of the displacement interaction is limited since warfarin has a very low hepatic extraction ratio and a long equilibrium time.[34]

Metabolism-related drug interactions

Drug interactions relating to metabolism involve the inhibition or induction of metabolising enzymes, most commonly cytochrome P450 (CP450) enzymes.[20] In terms of anticoagulant agents, warfarin, rivaroxaban and apixaban are CYP450 substrates and are thus susceptible to metabolism-related drug interactions.[9] Dabigatran is cleared renally in the unchanged form, and is therefore not involved in metabolism-related drug interactions.

Rivaroxaban and apixaban are metabolised hepatically via the CYP3A4 enzyme.[9] Co-administration of these factor X inhibitors with strong CYP3A4 inducers (such as rifampicin) may decrease the plasma concentration of the factor X inhibitors.[9,11] Combination of rivaroxaban and apixaban with CYP3A4 inhibitors is usually only significant when the CYP3A4 inhibitor also inhibits P-glycoprotein-mediated intestinal efflux (e.g. ketoconazole and ritonavir).

Warfarin is a racemic mixture of two enantiomers, the S-enantiomer is metabolised by CYP2C9, and the R-enantiomer is metabolised by CYP1A2, CYP2C19 and CYP3A4.[9] The S-enantiomer is more active (two to five-fold) than the R-enantiomer, thus interactions involving the S-enantiomer may be more significant.[9,35] Interactions which involve inhibition or induction of CYP450 enzymes responsible for the metabolism of both the S-enantiomer and R-enantiomers are of the greatest significance.[35]

Inducers of CYP450 enzymes involved in warfarin metabolism, may increase the clearance of warfarin, thereby impeding the anticoagulant activity.[9] Inhibitors of CYP450 enzymes involved in warfarin metabolism may decrease the clearance of warfarin, thereby enhancing the anticoagulant effect and increasing the patient's risk of bleeding.[9]

Drug interactions relating to the metabolism of warfarin can be managed through close INR monitoring and dose adjustments. The approach to managing the interaction requires insight into the time of onset and termination of the drug interaction, as well as the expected impact of the interaction on the effect of warfarin.

Interactions resulting from the inhibition of enzymes have a more rapid onset and offset compared to interactions resulting from the induction of enzymes. Thus, INR monitoring when starting or stopping a drug that inhibits warfarin metabolism, should take place within the first 3–5 days of co-administration (except for the long-acting agent amiodarone, which should be monitored one week into co-administration).[35] When starting or stopping a drug that induces the metabolism of warfarin, INR should be monitored weekly to detect a potentially delayed onset of the interaction.[35]

Pharmacodynamic drug interactions

All oral anticoagulant therapy can be subject to pharmacodynamic drug interactions, which can either result in additive or diminished effects of the anticoagulant. Co-administration of oral anticoagulants with antiplatelet therapy, nonsteroidal anti-inflammatory drugs (NSAIDs) and serotonergic agents result in an additive risk of bleeding as an adverse effect.[35] Warfarin is also subject to an additive drug interaction with paracetamol, particularly when co-administered for several days and when the paracetamol daily dose exceeds 2 g per day.[9] The interaction with paracetamol is unique to warfarin, and does not occur when NOAC agents are co-prescribed with paracetamol.[11]

Combining anticoagulant agents with antiplatelet therapy may increase the risk of bleeding. Although the risk for bleeding is significant with the combination of oral anticoagulant and oral antiplatelet therapies, it is important to consider the clinical relevance of this drug interaction in relation to patient-specific factors. There are compelling indications for the combination of anticoagulants and antiplatelets, in which case the benefit of combining therapy outweighs the risk for additive adverse effects.[35]

An example of an opposing pharmacodynamic drug interaction involves the co-administration of warfarin with combined oral contraceptive agents. This drug interaction significantly increases risk for thrombosis (4–5-fold compared to placebo) when warfarin and combined oral contraceptives are combined.[9,11] The risk for this pharmacodynamic interaction with NOACs is not as well documented.[11]

Summary of drug interactions

In summary, all oral anticoagulants can potentially be involved in drug interactions. Thus, when assessing the appropriateness of the chosen oral anticoagulant for a patient, pharmacists need to consult reliable resources to investigate for potential drug interactions, for example, IBM Micromedex, the South African Medicines Formulary and EM Guidance.[5,6,11]

Special population groups

Chronic kidney disease

The safety of anticoagulant use in chronic kidney disease (CKD) patients is of particular concern, not only because of the need to adjust anticoagulant doses, but also because CKD patients exhibit a higher inherent bleeding risk than patients with normal renal function.[36] Thus, when a CKD patient requires anticoagulant therapy (for example, for VTE prophylaxis in atrial fibrillation), careful clinical consideration is required to balance the VTE and bleeding risk in the patient.[37]

Prior to the availability of NOACs, CKD patients requiring anticoagulation were treated with low doses of warfarin. The use of warfarin in severe CKD is complicated by the high incidence of vitamin K deficiency associated with renal disease.[36] Furthermore, despite the use of low doses, maintaining a therapeutic INR in CKD patients poses a challenge.[36]

The use of NOACs in CKD patients has the potential for accumulation and increased bleeding risk, since all NOACs are renally cleared to some extent.[36-39] Nevertheless, NOACs are preferred to warfarin in patients with mild-to-moderate CKD (GFR 30–49 ml/min).[38-40] This recommendation is based on the findings of the subgroup analysis of the RE-LY trial, which compared the safety and efficacy of dabigatran and warfarin in patients with a GFR of 30–49 ml/min. The subgroup analysis demonstrated similar efficacy but a lower risk for major bleeding with dabigatran use when compared to warfarin use.[39,41] Similar findings were demonstrated in the ROCKET-AF trial about rivaroxaban and in the ARISTOTLE study about apixaban.[39]

There is a lack of studies exploring the comparative efficacy and safety of warfarin and NOACs in severe CKD (CrCl 15–29 ml/min) and end-stage CKD (< 15 ml/min) patients.[39,40] Pharmacokinetic simulations informed approval of low doses of NOACS (except rivaroxaban) for patients with a GFR between 15–29 ml/min, however there is limited clinical efficacy or safety data to support these recommendations.[39,40] Thus, the use of anticoagulants and choice of agent remains a debate, necessitating an individualised multidisciplinary team approach when treating patients with end-stage CKD.[39] Recommendations for oral anticoagulant in renal impairment are summarised in Table III.[39,40]

Dosage adjustments for the NOACs (particularly dabigatran and rivaroxaban) are necessary when the GFR is less than 60 ml/min. Overall, NOACs are not recommended when the GFR is less than 15 ml/min.[39,40]

Liver disease

The use of anticoagulants in liver disease patients requires careful clinical consideration since advanced liver disease may increase the risk of bleeding or thrombosis due to the disruption in the production of both clotting factors and clotting inhibitors.[43] Furthermore, advanced liver disease may influence the elimination of anticoagulant drugs, affect the anticoagulant response, and predispose to drug-induced liver injury.[36]

Warfarin has traditionally been used in treating and preventing VTE in patients with liver disease.[43,44] However, liver disease patients present with intrinsically elevated INR readings, making warfarin dosing in these patients challenging.[36] Furthermore, there is a lack of rigorous clinical trials investigating the safety and efficacy of warfarin in liver disease patients.[45]

Table III: Recommendations for oral anticoagulant use in renal impairment[39,40]

GFR (ml/min)	Warfarin	Dabigatran	Rivaroxaban	Apixaban
> 90	Dose according to INR	No dose adjustment	No dose adjustment	No dose adjustment
60–90	Dose according to INR	No dose adjustment	No dose adjustment	No dose adjustment
30–59	Dose according to INR	Use with caution, reduce dose*	Use with caution, reduce dose*	No dose adjustment
15–29	Dose according to INR	Contraindicated	Use with caution, reduce dose*	Use with caution, reduce dose*
< 15	Dose according to INR	Contraindicated	Contraindicated	Contraindicated in South Africa (FDA has approved a reduced dose)

*Exact dose is dependent on indication and bleeding risk
GFR – glomerular filtration rate

Data on the safety and efficacy of NOAC agents in significant active liver disease is lacking because NOACs are excluded from major trials.[36,45] A meta-analysis which explored available literature on the use of warfarin and NOACs in patients with liver disease suggests that NOAC use may be associated with lower mortality, intracranial haemorrhage and embolism risk when compared to warfarin use.[43]

In conclusion, the choice and dose of the anticoagulant agent depend on the severity of the liver disease (Figure 3). Liver disease is categorised according to the Child-Pugh Score as either Class A, B or C (increasing severity of disease). All NOACs and warfarin can be safely used in patients with Class A liver disease.[45] NOACs, except rivaroxaban, can be used with caution in Class B liver disease, while warfarin is considered safe to use.[45] Only warfarin is recommended for use in Class C liver disease.[44,45]

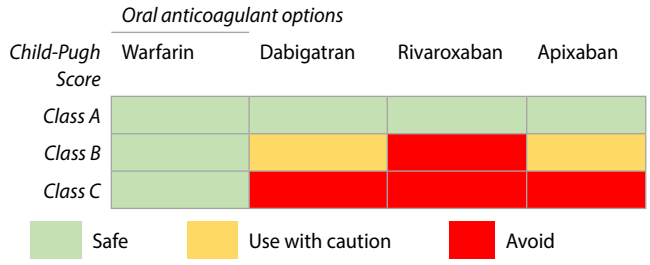

Figure 3: Anticoagulant suitability relative to liver disease severity[44,45]

Obesity

The efficacy and safety of oral anticoagulant therapy in obese patients (body mass index [BMI] greater than 30 kg/m^2) is of clinical relevance since obesity is associated with an increase in VTE risk.[46-49] Furthermore, obesity increases the risk of conditions associated with VTE, including atrial fibrillation.[46] Despite the importance of oral anticoagulant therapy in obese patients, there is limited data on the safety and efficacy of NOACs in this special population group.[46-50]

Obesity can potentially affect the distribution, metabolism and clearance of oral anticoagulants.[44,49] The volume of distribution of more lipophilic NOACs, such as dabigatran and apixaban, increases in obese patients.[44,47,50] This increase in the volume of distribution may result in a decrease in the plasma concentration of the drug.[44,50] The volume of distribution of rivaroxaban is less impacted by obesity.[47]

Renal perfusion and clearance are increased in obese patients, which may accelerate the elimination of oral anticoagulants.[46,51,52] Pharmacokinetic changes in obesity may affect the peak and trough concentration of NOAC agents.[46] There is a need for further studies to determine the clinical relevance of these pharmacokinetic changes in obesity.[47]

Safety and efficacy are important pharmacodynamic considerations when prescribing oral anticoagulants in obese patients. Studies have suggested improved safety of NOACs compared to warfarin use in obese patients regarding bleeding events.[49,50,53] A study focused on apixaban safety in obese patients also exhibited non-inferiority when compared to warfarin.[50] Furthermore, the results of a recent study suggest that obesity does not significantly impact the efficacy or safety of apixaban.[54]

Similarly, in terms of efficacy, NOACs have been found to be non-inferior when compared to warfarin,[46-48,50,55] with some researchers even suggesting that NOACs show superior efficacy in obese patients when compared to warfarin.[50,53]

Since there is limited evidence regarding the impact of obesity on the pharmacokinetics and pharmacodynamics of NOACs, it is generally advisable to use warfarin instead of NOACs in severely obese patients (BMI > 40 kg/m^2 or body weight> 120 kg).[46,47,55] If NOACs are to be used in severely obese patients, it is suggested to perform drug plasma concentration monitoring to guide dosing.[46,47] However, there are challenges associated with drug plasma concentration monitoring of NOACs, including poor availability, lack of therapeutic targets and lack of evidence on the correlation between plasma concentration and therapeutic outcomes.[47,55]

In conclusion, the lack of evidence on safety, efficacy and pharmacokinetic variability of NOAC use in obese patients limits the use of NOACs in severely obese patients.[46,48-50] It is preferred that severely obese patients are treated with warfarin.[46,55]

Conclusion

Pharmacists play a crucial role in ensuring the rational use of medicines, including anticoagulants. The choice of oral anticoagulant should consider the pharmacological and clinical characteristics of the drug options along with the individual patient needs.

In terms of efficacy, NOACs have been shown to be non-inferior compared to warfarin and possess a wider therapeutic window, decreasing the need for routine monitoring. Severe bleeding events occur more frequently with warfarin than NOACs; however, the limited availability of antidotes for NOACs is a concern (with only an antidote available for dabigatran).

NOACs offer several advantages in terms of their pharmacokinetic profile, such as a quick onset of action and shorter half-lives when compared to warfarin. However, the use of NOACs in special population groups (such as CKD, chronic liver disease and obesity) has not been extensively studied, which limits the availability of evidence-based recommendations for these patients.

When comparing warfarin and the NOAC agents, it is evident that there is no "ideal" agent which is preferable in all clinical settings. It is crucial that the multidisciplinary healthcare team promotes the rational use of anticoagulant therapy by considering patient-specific factors which may influence the safety and efficacy of

various oral anticoagulants. Pharmacists are able to contribute to rational anticoagulant use by providing recommendations in response to clinically significant drug-drug interactions, and drug-disease interactions (including renal and hepatic dose adjustments).

Conflict of interest

The author has no conflicts of interest to declare.

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Colds, flu and coughing: a review of over-the-counter cold and flu medicines

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Abstract

The common cold is the most frequent human illness, and may be caused by several families of viruses, particularly the more than 100 serotypes of rhinoviruses. Inaccurate perceptions that antibiotics improve patient outcomes fuel the number of doctor visits and requests for antibiotics. The inappropriate use of antibiotics for minor, self-limiting, usually viral, upper respiratory tract infections does not alter the course of the disease, and adds to the burden of antibiotic resistance. In addition, there is also no evidence to suggest that antibiotics prevent secondary bacterial complications following viral upper respiratory tract infections. While most over-the-counter (OTC) cold and flu remedies have no proven efficacy, they appear to attenuate the immune response to the infecting virus, and there is little doubt that appropriate symptomatic treatment can make the patient feel better. Therefore, symptomatic therapy remains the mainstay of common cold treatment. This article briefly reviews the components of cold and flu remedies, and provides a symptom-based assessment for the selection of appropriate OTC medicine.

Keywords: colds, flu, coughing

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Introduction

The constellation of a sore throat, rhinorrhoea, nasal congestion, coughing, low-grade fever, headaches and the malaise of the common cold, has been recognised as a disease entity since antiquity.[1,2] The common cold is the most frequent human illness, and is caused by members of several families of viruses. The most likely offenders are the ±100 serotypes of rhinoviruses.[2]

Many individuals seek medical care for uncomplicated upper respiratory tract infections.[2] A study conducted on US children revealed that 30% of these visits result in a prescription for antibiotics. Inaccurate perceptions that colds are caused by bacteria, or that antibiotics improve the outcome, fuel the number of visits and parental requests for antibiotics.[3] However, educational interventions by all healthcare professionals need to incorporate the suggestion that there is no cure for the common cold, other than allowing for the passage of time during which the infecting virus is cleared by the immune system. Indeed, it is the person's immune response, rather than the infecting virus, that is responsible for most of the symptoms of the common cold.[1]

Antiviral therapy is not available for most of the viruses that cause the common cold.[2] The inappropriate use of antibiotics for minor, self-limiting, usually viral, upper respiratory tract infections does not alter the course of the disease, but instead adds to the burden of antibiotic resistance.[2,4] There is also no evidence to suggest that antibiotics prevent secondary bacterial complications of viral upper respiratory tract infections.[1]

An appreciation that clear nasal secretions frequently become purulent without signifying bacterial infection, and that coughing is a normal symptom, is most important. Healthcare professionals should be familiar with the natural history of the common cold, so that any deviation from the norm is managed effectively (Figure 1).[4] The common cold is to be distinguished from influenza, pharyngitis, acute bronchitis, acute bacterial sinusitis, allergic rhinitis, and pertussis.[5]

Treating cold and flu symptoms

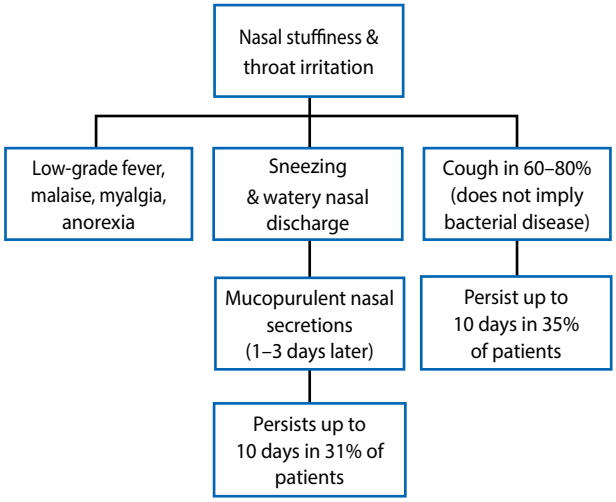
Most cold and flu medicines attenuate the effects of the person's immune response to the virus.[1] While most over-the-counter (OTC) cold medicines have no proven efficacy and potential for serious adverse effects,[2] there is little doubt that appropriate symptomatic treatment can make the patient feel better.[5] The placebo effect also plays an important role here.[5]

Therefore, symptomatic therapy remains the mainstay of common cold treatment.[6] However, symptomatic therapies have associated risks, particularly in young children.[2]

The recommendation from the US Food and Drug Administration (FDA) is that OTC medications should not be used to treat the symptoms of the common cold in children who are younger than six years of age.

Symptoms need not be treated unless they bother the child, e.g. by interrupting sleep, interfering with eating and drinking, or by causing discomfort.

If an OTC medicine is required for a child, it is recommended that single-ingredient medicines are used to treat the most troublesome symptom, and that proper dosing instructions are followed to avoid potential toxicity.[2]



Adapted from: S Afr Fam Pract. 2009;51(2):106

Figure 1: Natural history of the common cold

Polypharmacy abounds in the area of cold and flu remedies, and patients should not be overtreated. The recommended approach for adults is to select an appropriate treatment based on the patient's symptoms and available evidence, taking into account patient preferences (Table I).[5]

Symptom alleviators for colds and flu

Antihistamines

Antihistamines may reduce some of the symptoms of a cold, such as rhinorrhoea and sneezing. These effects are due to the anticholinergic effects of the older or first-generation antihistamines, such as chlorpheniramine, brompheniramine and promethazine.[5] However, antihistamines are not effective in reducing nasal congestion. Some first-generation antihistamines, e.g. diphenhydramine, are included in cold remedies for their

Sneezing, rhinorrhoea	Nasal congestion	Headache, fever
↓	↓	↓
Antihistamine	***Oral decongestants***	***Analgesics***
First-generation	• Ephedrine	• Paracetamol
• Chlorpheniramine	• Pseudoephedrine	• Ibuprofen
• Brompheniramine	• Phenylephrine	• Aspirin[b]
• Pheniramine	• Phenylpropanolamine	• Codeine
• Promethazine[a]		
• Diphenhydramine		
• Triprolidine		
• Phenyltoloxamine		
Second-generation		
• Loratadine		

Antihistamine	Decongestant[c]
Triprolidine plus pseudoephedrine, e.g. Actifed® Cold Tablets or Syrup and Betafed® Syrup)	
Chlorpheniramine plus phenylephrine, e.g. Demazin® Syrup	
Chlorpheniramine plus pseudoephedrine, e.g. Flusin® C Syrup	
Brompheniramine plus pseudoephedrine, e.g. Dimetapp® Paed Elixir	
Loratadine plus pseudoephedrine, e.g. Demazin® NS Repetabs	

Decongestant	Analgesic
Pseudoephedrine plus ibuprofen, e.g. Advil® Cold & Sinus Tablets, Benylin® Daytime Flu and Sinutab 3-way Tablets	
Phenylephrine plus paracetamol, e.g. Adco-Sinal® NS Capsules, Sinuclear® Capsules and Flutex® Junior Cold and Flu Syrup	
Phenylpropanolamine plus paracetamol, e.g. Sinuclear® Capsules	
Pseudoephedrine plus paracetamol, e.g. Sudafed® Sinus Pain Tablets, Sinugesic® Tablets and Sinumax® Tablets	
Pseudoephedrine plus paracetamol/codeine, e.g. Sinumax® with Codeine Tablets	

Antihistamine	Decongestant	Analgesic
• Triprolidine plus pseudoephedrine plus paracetamol, e.g. Acuflu® P Syrup and Adco-Flupain® Syrup		
• Diphenhydramine plus pseudoephedrine plus paracetamol, e.g. Benylin® 4 Flu Liquid/Tablets		
• Chlorpheniramine plus ephedrine plus paracetamol, e.g. Flusin® Tablets, Sinucon® Tablets and Sinuend® Tablets		
• Chlorpheniramine plus pseudoephedrine plus aspirin[b], e.g. Coryx® Effervescent Tablets		
• Chlorpheniramine plus pseudoephedrine plus paracetamol, e.g. Flusin® S Effervescent, Sinutab® Sinus Allergy Congestion & Pain		
• Chlorpheniramine plus phenylephrine plus paracetamol, e.g. Flustat® Capsules, Grippon® Capsules, Grippon® Cold and Flu Tablets, Histacon® Capsules		
• Phenyltoloxamine plus phenylpropanolamine plus paracetamol plus codeine, e.g. Adco-Sinal® Co Tablets		

a = Avoid giving to children under the age of 2 years, b = Do not give aspirin to children under the age of 16 years, c = Some products may also contain low doses of caffeine or vitamin C

antitussive action, or to help the patient sleep, when included in combination products intended to be taken at night.[5]

Evidence suggests that when used alone, antihistamines are of little benefit in treating the symptoms of the common cold, but that they may offer limited symptomatic relief when used in combination with decongestants, analgesics and cough suppressants.[5] Non-sedating antihistamines, such as loratadine, have been studied in combination with decongestants, and appear to decrease rhinorrhoea, sneezing and congestion, without causing drowsiness.[1]

Note: Promethazine-containing medicines are contraindicated for use in children under the age of two years.[7]

Decongestants

Nasal congestion that is associated with the common cold may be alleviated by topical and oral sympathomimetic (adrenergic) decongestants, such as xylometazoline, oxymetazoline, ephedrine, phenylephrine and pseudoephedrine.[5] Compared to placebo, a single dose of an oral or topical decongestant improves subjective nasal symptoms that are associated with a reduction in airways resistance.[6] However, topical decongestant use should be limited to two to three days, as rebound congestion may occur after 72 hours of use.[5,6]

Oral sympathomimetic decongestants, such as pseudoephedrine, are no longer available OTC in South Africa as single-ingredient products.

Various combination products are available (Table I)[8]:

- An oral decongestant in combination with a first- or second-generation antihistamine.
- An oral decongestant in combination with an analgesic, such as paracetamol, or a nonsteroidal anti-inflammatory drug, such as ibuprofen.
- An oral decongestant in combination with both an antihistamine and an analgesic.

Other components of cold and flu remedies

For many years, vitamin C has been touted as an effective agent for the prevention and treatment of the common cold.[1] High-dose vitamin C (> 1 g/day) has been shown to reduce the duration of colds by 8%.[5] However, the improvement in symptoms following the intake of high-dose vitamin C appears to be no greater than that seen with standard OTC cold remedies.[1]

Echinacea is a popular herbal cold remedy. Few modern studies support its efficacy. Prophylaxis studies suggest that echinacea has no significant effect in preventing rhinovirus infection.[1] Treatment studies show mixed results, with some studies showing some improvement in symptoms, while others show no improvement compared to placebo.[1]

Caffeine is included in some combination products to produce wakefulness and to offset some of the sedation caused by the first-generation antihistamine.[5] Doses of at least 100 mg are needed to produce such an effect. Most OTC products contain 30–50 mg per tablet, about the same as a cup of coffee.[5] It has also been claimed that caffeine increases the effectiveness of analgesics, but the evidence to support this claim is not definitive.[5]

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Insomnia: what is currently available

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Abstract

Insomnia is an important public health burden and is the most ubiquitous sleep disorder in the general population, requiring accurate diagnosis and effective treatment. Sleep hygiene and cognitive behavioural therapy form the foundation of management. In addition, various pharmacological entities are at hand to augment insomnia disorder. Acute insomnia requires short-term management with appropriately indicated hypnotic agents, while chronic sleeping difficulties benefit more from antidepressants. This article informs the reader about the currently available sleeping agents in South Africa, and may not include more effective or potent agents used in other parts of the world that are not yet accessible for local prescription.

Keywords: insomnia, antidepressants, antihistamines, benzodiazepines, melatonin, non-benzodiazepines

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Traditionally, insomnia is defined as the subjective perception of persistent difficulty in initiating, maintaining and achieving quality sleep which results in associated daytime impairment, notwithstanding sufficient opportunity or external environmental factors to do so.[1] Epidemiological surveillance studies from the general population illustrate that between 19% and 44% of adults experience some form of sleeping difficulty or abnormality, of which 10–15% of those conform to the official diagnostic criteria for insomnia according to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM V).[2] Incidence rates vary significantly between different countries and communities. The prevalence of insomnia and related symptoms is still poorly understood. However, factors such as sociodemographic conditions, health status and risk behaviour, stress, support systems, education, income, age and gender have all been previously described.[3] Nocturnal sleep problems seem to be present in approximately 30% of the South African population, with a slight predisposition towards females (31.3%) compared to males (27.2%).[4]

Insomnia disorder is often associated with comorbid psychiatric or medical conditions, including alcohol or substance abuse. For this inference, few studies are available to quantify the exact prevalence of insomnia as being the principal reason for visiting a general practitioner, yet independent observations tend to suggest approximately 10% of all GP visits are related to sleeping complications being the focus of the consultation.[5] Although insomnia is the most common sleeping disorder, it is estimated that only 50% of patients encountering sleeping difficulties consult their family physician or general practitioner for medical assistance or advice.[6] Insomnia is more prevalent in women and the older population and has been associated with high societal costs and lower quality of life scores, resulting in increased hospitalisations, physician visits and absenteeism. It is estimated that insomnia costs the US economy approximately $100 billion annually.[7]

The disorder is classified as either short term (acute) or chronic (long term) depending on the duration of symptoms. Short-term insomnia, also known as adjustment or acute insomnia, usually manifests in response to an identifiable stressor and symptoms do not exceed a period of three months. Chronic insomnia is diagnosed when symptoms occur at a frequency of at least three times per week and have been present for three months or longer.

Consequences of insomnia

When the normal sleep process is delayed or disrupted, it is natural to harbour feelings of stress, which in turn results in a vicious cycle of insomnia. Recuperative sleep is necessary for general physical health and mental agility. In addition, sleep quality has a direct effect on a person's productivity, emotional well-being, immune status and weight control. Although sleep requirements may vary individually, most healthy adults require at least seven hours of sleep per night to function at their best.[8] Sleep duration less than seven hours has been associated with a higher incidence of non-communicable chronic diseases such as obesity, hypertension, dyslipidaemia, metabolic syndrome (including diabetes), coronary heart disease, depression, and even colorectal cancer.[9] Excessive daytime sleepiness as a result of insomnia, sleep loss, sleep fragmentation or shift work is responsible for nearly 20% of all traffic accidents and sleep-related fatalities in individuals sleeping less than five hours in a 24-hour cycle.[10]

Overview of pharmacological modalities

An abundance of pharmacological and non-pharmacological treatment options are available for various types of sleeping disorders. However, sleep hygiene advice and stimulus control form the pillar in managing both short- and long-term insomnia. Cognitive behavioural therapy (CBT) is regarded as the first-line treatment for insomnia. Nonetheless, this requires specialised settings and is not easily available to many patients dependent

on South Africa's public healthcare system. For this reason, pharmacological approaches are mostly used in the clinical setting.[11] Hypnotics are regarded as having the best short-term efficacy, while antidepressants are considered the best option for managing long-term sleep disorders.

Treatment comparisons regarding sleep-onset latency (SOL) (the amount of time it takes from being fully awake to sleep), wakefulness after sleep onset (WASO) (periods of wakefulness occurring after defined sleep onset) and the amount of total time spent sleeping, are often used to decide which hypnotic is best suited for a specific sleeping disorder. A presumably short-acting drug with a duration of < 8 hours is recommended in patients with sleep-onset insomnia or those having difficulty falling asleep (zolpidem or triazolam). Patients with sleep maintenance insomnia, or those waking up in the middle of the night require longer acting drugs such as zolpidem extended release, zopiclone, temazepam, or lorazepam. Table I illustrates the indirect comparisons of the available hypnotic agents in South Africa and represents averages of the oral dosage forms and strengths, since sleep parameters differ significantly between individuals.

Table I: Indirect comparison of half-life, sleep-onset latency and total sleeping time of available South African hypnotics

Drug	T1/2 (hours)	SOL (minutes)	Total sleep time (hours)
Benzodiazepines			
Short acting			
Triazolam	2–3	26.7	6.7
Midazolam	1.5–2.5	25.3	7.1
Intermediate acting			
Oxazepam	10–20	14.9	7.4
Lorazepam	10–20	34.6	7.4
Loprazolam	7–8	37.1	7.3
Alprazolam	12–15	8.6	7.5
Temazepam	10–40	16.7	7.7
Long acting			
Flurazepam	40–100	45.4	6.8
Diazepam	20–80	19.7	7.4
Nitrazepam	35–45	27.2	8.1
Non-benzodiazepines			
Zolpidem	3	12.8	7.5
Zopiclone	5	11	7.1
Melatonergic agents			
Melatonin	0.5–1	8.3	3.5
Antidepressant drugs			
Trazodone	10–12	26.2	6.7
Mirtazapine	20–40	11.7	6.9
Amitriptyline	20–30	37.7	5.9
Antihistamines			
Diphenhydramine	4–6	34.2	6.6
Doxylamine	10–15	52.5	N/A

SOL – sleep-onset latency

Pharmacological strategies

Any approved pharmacological class of sedatives and hypnotics is superior to placebo in improving short-term sleep outcomes and effectivity. However, the potential benefits of pharmacotherapy remain debatable due to post-marketing pharmacovigilance reports, overestimation of risk/benefit ratio, addiction potential, sleep quality and daytime function, to mention a few.[1] Although various drug groups are employed worldwide, only the currently available agents on the South African market indicated for sleeping disorders will be further discussed.

Benzodiazepines

Benzodiazepines have been available for treating insomnia since the mid-1950s. These drugs act as agonists at γ-aminobutyric acid ($GABA_A$) α1, β and γ neuroreceptors and have far less overdose danger and abuse potential than barbiturates and opioids used for sleep.[12] Benzodiazepines are beneficial in increasing the sleeping time and improving the quality of sleep by reducing the SOL and wakefulness after sleep onset.[13] Most benzodiazepines are extremely effective in inducing sleep, but are frequently associated with ataxia, sedation, daytime drowsiness and cognitive impairment.[14] All benzodiazepines can result in respiratory depression, especially in patients with pulmonary disease. Tolerance and addiction develop quickly with continuous use. Agents such as flurazepam and diazepam have active metabolites with extraordinarily long half-lives which can last up to 11 days. This makes them unfavourable to prescribe in elderly patients, as falls with hip fractures can result. Recently it has been shown that taking benzodiazepines with half-lives exceeding 20 hours, or chronic administration for periods longer than three years have a significantly increased risk for developing Alzheimer's disease.[15] Withdrawal from long-acting agents can be difficult, causing an initial syndrome of insomnia followed by persistent anxiety, depression, nausea and perceptual changes (hallucinations) extending beyond the half-life of the agent for up to three weeks. Withdrawal from short-acting agents has similar symptoms but may develop within a few hours after discontinuation.[16]

Non-benzodiazepine hypnotics

Non-benzodiazepine drugs, also known as "Z" drugs (zolpidem and zopiclone) are chemically dissimilar to the traditional benzodiazepine agents. They are still referred to as "newer" sedative-hypnotics, although some of them (zolpidem) have been available for almost 26 years.[17] These agents slow brain activity by selectively binding to the α1 subunit of the $GAGA_A$ receptor which is primarily responsible for the sedative/hypnotic activity of benzodiazepine drugs.[18] Their lack of binding to other $GABA_A$ subunits (β and γ) makes them a popular choice in treating adults who have difficulty in falling asleep or staying asleep. Unlike traditional benzodiazepines, the Z drugs have minimal impact on sleeping stages and do not display REM sleep rebound. In addition, their receptor selectivity ensures a more favourable side effect profile regarding the development of tolerance and the potential for dependence. Z drugs are metabolised by the liver

ZOPISLEEP 7,5 mg

Zopiclone

S5 Reg. No.: A37/2.2/0375, Zopisleep 7,5 mg Tablets. Each tablet contains 7,5 mg Zopiclone. **Class:** A2.2. Sedatives, hypnotics.
Applicant: iPharma (Pty) Ltd. 124 Elevation Avenue, Randjesfontein, Midrand, 1683, South Africa
Ph +27 (0)11 314 2366 Fax +27 (0)86 600 6315 info@ipharma.co.za Co. No.: 2010/000192/07;
Marketed by: Arya Pharma (Pty) Ltd. Co.No.: 2015/413329/07. DOP: February 2021 Advert code: A0043/02/21.
For full prescribing information refer to the package inserts approved by the medicines regulatory authority.

and the dosage needs to be adjusted in hepatic dysfunction or the elderly. None of these agents should be used during pregnancy or lactation.

Zolpidem and zopiclone may cause impaired memory and psychomotor retardation. Recent reports on the safety of non-benzodiazepine drugs have resulted in updated black box warnings cautioning against sleepwalking, sleep driving and engaging in any other activities while not fully awake after taking these medicines. Patients with a prior history or those experiencing any complex adverse sleep behaviour, even after a single dose, should abstain from future ingestion of the offending agent, although the incidence is very rare. Physicians should initiate treatment with the lowest dose possible for the shortest period of time.[19]

Melatonergic drugs

Insomnia resulting from disruptions in the circadian rhythm where endogenous melatonin levels do not naturally increase before sleep onset (such as jet lag, shift work or old age) may benefit from melatonin extended-release agents. Melatonin is beneficial in increasing the total sleeping time and decreasing onset of sleep in patients older than 55 years, children suffering from autism spectrum disorder or attention-deficit/hyperactivity disorder, patients with depressive disorders and females with premenstrual dysphoric disorder.[20] These drugs act as chronobiotics and are capable of shifting the phase of the circadian timing system to mimic the natural endogenous melatonin release required to activate pathways responsible for sleep initiation.[21] Until recently, melatonin was available as an over-the-counter (OTC) agent, but has been rescheduled to Schedule 4, necessitating a prescription. Side effects are uncommon but may include blood abnormalities (leukopenia, thrombocytopenia), CNS side effects, visual disturbances and drug interactions by inducing CYP3A hepatic isoenzymes.[22]

Antidepressant drugs

Sedating antidepressants are often used off-label to treat insomnia. For this reason, dosing recommendations and guidelines are unavailable, and the tolerability and safety of these agents are unknown. The most commonly used antidepressants in sleeping disorders are mirtazapine, trazodone and amitriptyline. Subtherapeutic antidepressant doses of trazodone have been reported to cause an improvement in sleep quality, and despite a lack of guidelines, remains the second most frequently prescribed agent (following zolpidem) for insomnia in the USA.[23]

Low doses of tricyclic antidepressants (TCA), such as amitriptyline, are useful in managing chronic pain that may be responsible for sleep disturbances. Insomnia caused by depression will additionally find benefit from TCAs. Similarly, mirtazapine, a noradrenergic and specific serotonergic agent with significant antihistaminergic properties, is beneficial in patients with comorbid depression. In general, these antidepressants produce sedation by blocking acetylcholine, noradrenaline and serotonin presynaptic receptors with mainly urinary retention and hypotension as adverse effects.[23] The use of antidepressants for insomnia could be justified in chronic treatment when long-term use of benzodiazepines would potentially result in tolerance and addiction.

Sedating antihistamines

Sedating H_1 antihistamines (diphenhydramine and doxylamine) are available as OTC medication, but have a negligible effect on sleep quality compared to benzodiazepines. They have a significant affinity for other receptor subtypes, including muscarinic receptors resulting in severe anticholinergic side effects (dry mouth, blurred vision, constipation and confusion).[24] Older individuals are more prone to these effects and they are more pronounced with longer acting agents such as doxylamine. Tolerance to the effects of diphenhydramine develop within a week. The most useful off-label clinical utility of antihistamines may be argued in patients with associated allergic symptoms or upper respiratory infections causing insomnia. Currently, antihistamines are not recommended for insomnia due to the lack of demonstrated efficacy and high incidence of adverse effects.[1]

Conclusion

Insomnia is a common condition experienced by males and females from every age group, but healthcare practitioners often underestimate its prevalence. Pharmacists need to actively ask patients about insomnia symptoms and encourage good sleep hygiene practices. In the short term, insomniacs can be effectively managed by a combination of pharmacological and non-pharmacological modalities. Pharmacological treatment with benzodiazepines or benzodiazepine-like agents should not exceed two to four weeks. Antihistamines and antidepressants should be used with caution due to their anticholinergic side effects. The diagnosis and treatment have a high functional success rate and clinicians need to harbour a greater awareness in the clinical evaluation and management of insomnia. In addition, pharmacists need to embrace the evidence that non-pharmacological treatment is superior in the long-term management of sleeping disorders and take note that hypnotics should not be prescribed for continuous periods.

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An update on oral opioids for the management of pain

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Abstract

Pain is an uncomfortable experience associated with various pathologies, including cancer. Advances in medical science have allowed for the development of effective analgesics, and opioids are the most effective in combating pain. Concerted efforts from healthcare workers and an understanding of the characteristics of different opioid drugs are cardinal in the effective use of these chemical entities in the effective management of pain. This short review focuses on discussing the currently available opioids for the management of pain.

Keywords: pain, opioids

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Pain

Definition

According to the International Association on the Study of Pain, pain can be defined as "an unpleasant sensory and emotional experience associated with, or resembling that associated with actual or potential tissue damage".[1] Although the acknowledgement of pain as a pathological entity in its own right is debated,[2] it poses a huge burden in the healthcare system.[3] The continuous rehabilitation of patients with pain sensations, hinders them from conducting day-to-day activities, which has a detrimental effect on the economy.[3] According to the Global Burden of Disease Study in 2016, pain and pain-related pathologies are a leading cause of disease burden and disability.[4] The study further reaffirmed that the global burden caused by pain is increasing, as 1.9 billion people were found to have recurrent-type headaches.[4]

Types of pain

Pain can be classified according to the pattern of occurrence's duration into acute and chronic pain.[3] Acute pain is temporary, and typically results from specific stimulus (chemical, thermal and mechanical). The four classic features of acute pain are that it is time-limited, has a triggering event, has a sudden onset, and can potentially develop into a pathologic condition.[5] In contrast, chronic pain persists for three to six months beyond the expected time frame. Chronic pain can either be intermittent or continuous and may persist regardless of the presence of any obvious stimuli or pathology. Cancer and associated surgery, chemotherapy or radiotherapy can result in a debilitating amount of pain, known as chronic malignant or cancer pain.[6] On the other hand, chronic pain resulting from other pathologies is known as chronic non-cancer or non-malignant pain.[6]

Alternatively, symptoms, mechanisms and syndromes can be used to classify pain into nociceptive, neuropathic, and inflammatory pain.[7] Neuropathic pain occurs as a response to actual or potential damage to visceral and somatic, non-neural tissue. Such stimuli activate nociceptors (Aδ- and C fibres), which are ultimately responsible for detecting chemical, mechanical and thermal stimuli.[3] Neuropathic pain is associated with nerve damage or nerve impairment and is commonly associated with allodynia – a central pain sensitisation that happens due to repetitive non-painful stimulation of receptors. Such sensitisation triggers a pain response to stimuli that normally does not provoke pain.[3] The inflammatory process is a natural response to tissue damage, that serves to remove necrotic cells and initiate the tissue healing process.[8] Upon tissue injury, neutrophils gather at the site of inflammation, followed by the release of chemical mediators. Such chemical mediators interact with nociceptors in the inflamed area, leading to inflammatory pain. Inflammation can result in allodynia, hyperalgesia or sympathetic maintained pain.[8]

Pain pathways

Pain is perceived in three stages, namely transduction, transmission, and modulation.[3] Following the presence of a noxious stimuli, nociceptors in the peripheral primary afferent fibres located alongside the spinal cord's dorsal root ganglia are activated. The transmission of pain signals occurs via two routes, the ascending and the descending pathways.[3] Transduction and transmission are major events in the ascending pathway. During transduction, noxious stimuli are converted from chemical events into electrical events that get subsequently transduced in the form of chemical neurotransmitters (substance P, glutamate, and other excitatory neurotransmitters) onto primary and secondary neurons in the spinal cord. Following transduction, electrical events are transmitted along the neuronal pathways, through the thalamus into the somatosensory cortex of the brain, leading to the perception of pain.[3]

In the descending pathway, spinothalamic nerves go downwards from the midbrain brain periaqueductal grey (PAG) via the spinal

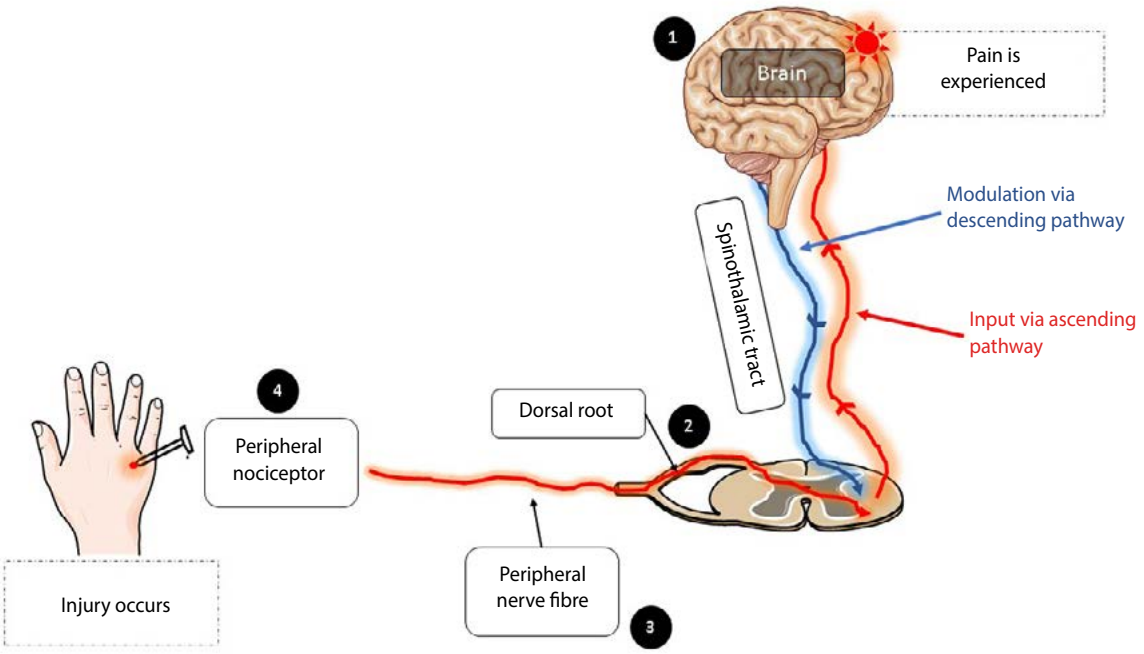

Figure 1: Adapted diagram showing the pain pathways and various targets for treatment options.[9] The target sites of the various treatment options are: (1) Opioids and α_2-adrenergic agonists in the brain; (2) Opioids, local anaesthetic agents and α_2-adrenergic agonists at the dorsal horn; (3) Local anaesthetics peripheral nerve fibre; (4) Local anaesthetics agents and non-steroidal anti-inflammatory drugs at peripheral nociceptors.

cord to the effector organs. Some AB fibres from peripheral tissues are also involved in the descending pathway.[3] The modulation of pain is facilitated through the inhibition of the spinothalamic tract by large fibres that impinge these neurons. Inhibition of the AB fibres stimulates the release of Mer-enkephalin from interneurons in the spinal cord.[3] Additionally, serotonergic fibres arising from the nucleus magnus raphe (NMR) release serotonin and norepinephrine fibres arising from the locus ceruleus (LC) release norepinephrine. When both these neurotransmitters are released, they inhibit the dorsal spinal neurons that transmit pain to the supraspinal structures. The pain pathways and various therapeutic targets are briefly outlined in Figure 1.

The elucidation of pain pathways and the physiology underlying pain has allowed for the development of analgesic agents. In the 1980s, the World Health Organization (WHO) developed a three-step ladder that has been used as a guideline for the pharmaceutical management of pain.[10] A major limitation of the initial guidelines is that they did not incorporate non-pharmacological interventions. The lack of consideration of alternative non-pharmacological strategies such as minimally invasive treatment can result in the irrational use of pharmacological agents (especially opioids), leading to unwanted side effects. As such, a revised four-step ladder that incorporates non-pharmacological treatments in conjunction with opioids and other analgesics has been proposed (Figure 2).[10]

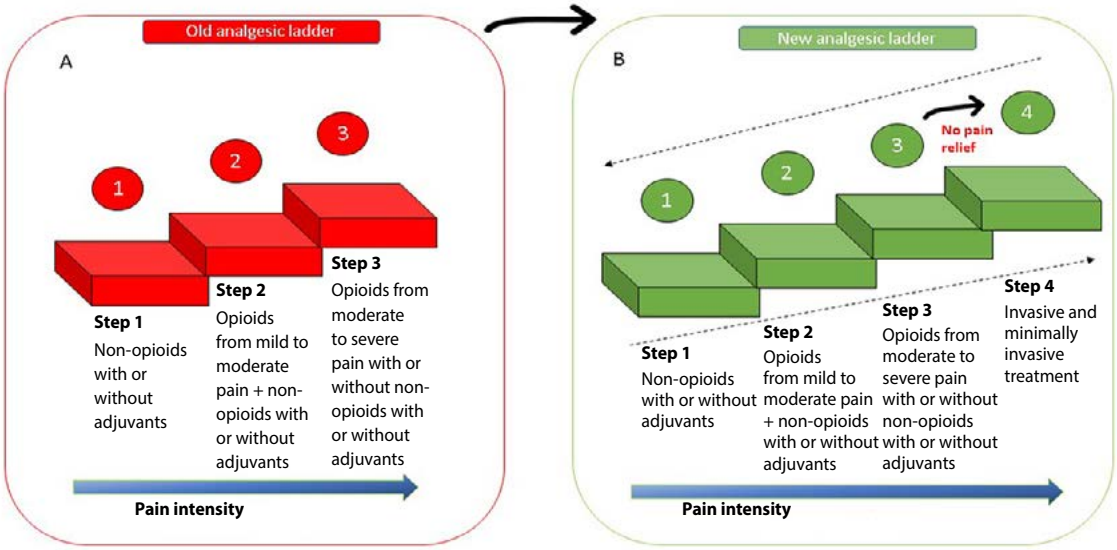

Figure 2: Transition from the initial WHO (A) three-step ladder to the (B) four-step ladder used as a guideline for the treatment of pain[10]

As shown in Figure 2, opioids are critical in the management of mild to moderate and severe pain. However, abuse and use-dependence preclude the optimal use of opioids in the management of pain.[11] This review aims to discuss oral opioids in the management of pain.

Mechanism of action of opioids

Opioid receptors

Opioid receptors are G protein-coupled receptors that are widely distributed in the brain, spinal cord, gastrointestinal tract, and skin.[12] There are three types of opioid receptors, the delta (δ), kappa (κ) and mu (μ) receptors.[13] Opioids and many metabolites bind to opioid receptors in the brain, leading to euphoria, respiratory depression and analgesia.[12] Although all three opioid receptors elicit an analgesic effect on the brain, they individually have distinct outcomes and distribution in various brain regions.[12] The μ receptors are found in the PAG, cerebral cortex, and thalamus, where they bind to endorphins and stimulate euphoria, use dependence and respiratory depression.[14] The δ receptors located in the PAG and hypothalamus bind to dynorphins to stimulate sedation and dysphoric effects.[14] The κ receptors are found in the basal ganglia, where they bind to enkephalins to induce an anxiolytic effect.[14]

Mechanism of opioid analgesia

Upon binding to receptors, opioids can modulate intracellular calcium disposition and alter protein phosphorylation.[15] Opioids exert their analgesic activity both pre- and postsynaptically. At the presynaptic level, they block the voltage-gated Ca^{2+} channels on afferent fibres. Consequently, neurotransmitters that contribute to nociception (e.g., substance P, serotonin, and glutamate) are reduced, leading to analgesia.[15] Postsynaptically, opioids result in the opening of K^{+} channels, leading to hyperpolarisation of neurons. This leads to decreased neuronal excitability, which ultimately results in analgesia.[15] Some opioids can inhibit serotonin uptake through various mechanisms, therefore, caution should be taken when administering opioids to patients already taking medication with serotonergic activity. Additionally, some opioids such as methadone act on the N-methyl-D-aspartate (or NMDA) receptors, where they antagonise glutamate. This is possibly why methadone has superior efficacy in combating neuropathic pain, compared to other opioids.[16]

Morphine

Morphine is one of the several important alkaloids derived from the poppy plant, *Papaver somniferum*.[17] The drug has remarkable efficacy in the relief of moderate to severe pain and serves as a standard by which other analgesic agents are measured.[17] Preoperatively, morphine is used to reduce anxiety, reduce the anaesthetic dose, and cause sedation.[17] Due to its vasodilatory and bradycardic activity, morphine is used in the treatment of myocardial infarction. Tolerance, physical dependence, respiratory depression, gastrointestinal effects at therapeutic doses are common side effects associated with morphine.[17] As a result, morphine is subject to abuse and is tightly controlled by national and international regulatory agencies.[17]

Hydromorphone

Hydromorphone is a hydrogenated semi-synthetic opioid agonist, with potent activity on the μ receptors, and weak activity on the κ opioid receptors.[6] Hydromorphone is used in the treatment of moderate to severe pain. Due to alterations (a keto-group instead of the hydroxyl group at position 6), hydromorphone is 5 to 10 times more potent compared to morphine, and has better distribution to the central nervous system, leading to enhanced analgesic activity.[18]

Although injections, oral solutions, suppositories and powder formulations are available in the USA, OROS®, a controlled-release oral hydromorphone formulation is the only formulation currently approved in the South African market (4 and 8 mg Jurnista®).[6] This formulation allows for the maintenance of constant plasma concentration levels of the drug, ensuring prolonged analgesia. In comparison to morphine, hydromorphone is better absorbed orally, and has a faster onset but shorter duration of action. This can be used as an advantage when trying to achieve short-term analgesia.[18] Compared to morphine and other opioids, hydromorphone has a similar side effect profile, however, euphoria, nausea, vomiting and constipation may be less pronounced.[6,19]

Oxycodone

Oxycodone is a semi-synthetic opioid used to treat moderate to severe pain. Oxycodone has strong agonistic activity at the κ receptors, and to a lesser degree, at the μ receptor.[20] Despite the use of oxycodone in combination with paracetamol for many years, it has been demonstrated that oxycodone may be safe and efficacious when used alone.[6] There are two main formulations of oxycodone; an immediate-release (conventional) preparation, and an extended-release preparation.[21] The conventional formulation can be used orally for the treatment of moderate to severe pain in conditions such as bursitis, dislocations, and postoperative, post-extraction and postpartum pain.[6] This formulation is available in oral capsules, with doses of 5, 10 and 20 mg.[6] It has a 10–15 minute onset of action, and a 3–6 hours duration of action.[6] The extended-release preparation is used in the treatment of moderate to severe pain, where continuous analgesia is required. This formulation maybe be advantageous in the treatment of cancer-associated pain, and for treating pain during rehabilitation.[6] The preparations for the extended-release formulation may be available in 10, 20, 40 and 80 mg strength. This formulation has a 1-hour onset of action and analgesic action can last up to 12 hours.[6]

Fentanyl

Fentanyl is a narcotic analgesic that was developed in the 1950s and 1960s in an effort to produce opioid analgesics with greater potency, analgesic efficacy, and fewer side effects compared to morphine.[22] Only injections and the transdermal formulations are registered in South Africa, however, a transmucosal immediate-

release (TIRF) formulation is available in other countries.[6] These short-acting fentanyls are delivered through sublingual (100, 200, 300, 400, 600 and 800 µg) and buccal tablets (100, 200, 400, 600 and 800 µg), intranasal sprays (100 µg/100 µL and 400 µg/100 µL) and troche/lozenges (200, 400, 600, 800, 1 200 and 1 600 µg).[6] These formulations are primarily indicated for the treatment of breakthrough cancer pain, in patients that are routinely taking other opioids for pain.[23] To mitigate the potential of abuse, misuse and addiction, TIRF preparations are administered to selected patients through the Risk Evaluation and Mitigation Strategy program of the United States Food and Drug Administration.[6]

Buprenorphine

Buprenorphine is an opioid derivative with higher potency (25–40 times) and has longer lasting analgesic effects compared to morphine.[24] The drug acts as a partial agonist at µ receptors, where it binds with great affinity but with low intrinsic activity.[24] It also has partial agonist effects at the κ receptors and is an antagonist at the delta receptors.[6] The rate of dissociation from the µ-receptors is slow, which results in an antagonistic effect to any other opioids that may be co-administered with buprenorphine.[24] Due to such antagonistic activity, buprenorphine is an effective treatment for opioid use disorder.[25] Approved oral preparations include a buprenorphine/naloxone tablet (2/0.5, 0.7/0.18, 1.4/0.36, 2.9/0.71, 5.7/1.4, 8.6/2.1, 11.4/2.9 mg/mg).[25] Constipation, asthenia, drowsiness, nausea and vomiting, fainting and dizziness, orthostatic hypotension, sweating, headaches, and insomnia are the most common side effects associated with buprenorphine use.[6]

Tilidine

Nortilidine, the main active metabolite of the opioid drug tilidine, has a high affinity to µ-receptors, but not to δ- or κ-receptors, and has typical opioid effects and side effects.[26] Tilidine is indicated for postoperative and severe pain, and is usually considered prior to stronger opioids.[27] Tilidine is available as Valoron® drops for use undiluted perilingually or sublingually with or without sugar.

Tramadol

Tramadol is a centrally-acting opioid analgesic that has a multimode of action. In addition to acting as an agonist at the µ receptors, tramadol also acts as a noradrenaline reuptake inhibitor.[28] Tramadol is indicated for the treatment of moderate to severe pain, and does not cause much serious adverse side effects when compared with other opioids like morphine.[28] Although other formulations of tramadol exist, oral preparations include; Tramal® 50 mg capsules and 100 mg sustained-release tablets, Austell-tramadol® 50 mg capsules, Dolatram® and Domadol® 50 mg capsules, Tramahexal® 50 mg capsules, and Tramaspen® and Tramazac® 50 mg capsules. Tramadol is also available in combination with paracetamol as Tramacet® at a dose of 325 mg/37.5 mg respectively.[28]

Tapentadol

Tapentadol is a newer opioid that has dual activity as a µ receptor agonist, and a noradrenaline reuptake inhibitor.[6] In comparison to other opioids like morphine, tapentadol resembles tramadol the most and similar multimode mechanism of action. However, in contrast with tramadol, tapentadol additionally inhibits the reuptake of norepinephrine. Consequently, tapentadol has an additional anti-nociceptive activity at the descending pathway, by reducing the transmission of pain signals to the brain.[29] Although not currently registered in South Africa, tapentadol is available in the form of tablets and film-coated tablets with modified release patterns under the trade name Palexia.[30]

Conclusion

Pain is a devastating experience and has a detrimental effect on patients suffering from it, and poses a huge burden on the healthcare system. Fortunately, advances in medical science have allowed for the elucidation of the mechanisms driving pain, which has led to the development of effective analgesics. Opioids form a cardinal part of the pain treatment ladder proposed by the WHO, as they are effective treating moderate to severe pain. However, due to the wide distribution of opioid receptors, opioid drugs are associated with various side effects, and the most concerning ones are use dependence and addiction. This short review highlighted the different oral opioids available. Each opioid drug has its unique mechanism of analgesic action and side effect profile. Where possible, the use of opioid analgesics should be limited when invasive and minimally invasive approaches can result in analgesia. This will strengthen the patient's experience of symptomatic relief, while side effects are avoided.

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Effective chronic pain management using wearable, pulsed shortwave therapy

Adcock Ingram South Africa announces the launch of a wearable, pulsed shortwave therapy (PSWT) device set to give South Africans living with chronic pain a new lease on life

Introduction

Globally, an estimated 20% of individuals are affected by chronic pain.[1] A recent local study showed a similar trend – estimating that one in five South African adults is affected by chronic pain.[2] Chronic pain accounts for 15–20% of visits to physicians.[1]

The International Association for the Study of Pain (IASP) defines pain as 'an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage'.[3] Chronic pain is defined as pain that lasts more than three to six months.[1]

Osteoarthritis, back pain, and headaches are the top three causes of chronic pain.[4] Chronic pain negatively impacts patients' quality of life (QoL)[2] and is also associated with significant direct (e.g., doctors' visits and medications) and societal costs (e.g., provision of medical care, social grants, and caregiver burden).[2]

How is chronic pain diagnosed?

According to the IASP, pain is 'always a personal experience that is influenced to varying degrees by biological (e.g., genetics, age, gender, hormones[4]), psychological (e.g., depression, anxiety[4]), and social factors (e.g., low educational, culture, poor social support[4]).[3]

Diagnosis is often complicated because pain is a personal experience. According to Carnago et al. there is no perfect diagnostic algorithm for chronic pain.[5] However, physicians should discuss and address their patient's pain with empathy and a desire to help.[5]

Dydyk and Conemann recommend starting with a history and physical examination. Important questions to ask include for example when the pain started, the frequency, what symptoms the patient experiences (e.g. muscle spasms or aches), temperature changes, restrictions to range of motion, morning stiffness, weakness, changes in muscle strength, changes in sensation, and hair, skin, or nails, and what factors result in the relief or worsening of pain.[6] Furthermore, pain scales (numbered from 0–10) can be used to measure the severity or intensity of pain.[6] The authors also recommend neurologic testing, as well as examining the area/location of pain.[6]

ActiPatch® Medical Device – Musculoskeletal Pain Relief. Pack shot

Another valuable diagnostic tool is a pain inventory, which can be used to determine to what extent pain impacts a patient's activities of daily living.[6] Although blood tests are not required, they may be valuable for diagnosis of potential causes of pain.[6]

How is chronic pain managed?

Carnago et al. stress that physicians can and should provide quality chronic pain management to patients in whatever setting they practice.[5]

According to Mao et al., managing chronic pain is 'to fight a war, not a battle'.[7] Mao et al. stress that when managing chronic pain, it is important to set realistic expectations and to inform patients that there are no quick fixes.[7] Effective management requires long-term strategies.[7]

According to the 2022 Centers for Disease Control and Prevention pain guideline, prescription opioids have been the mainstay of treatment for many years, even though long-term efficacy data (> 1-year) is limited.[8]

The authors of the guideline caution that long-term opioid use is associated with increased risks of overdose, misuse, all-cause deaths, fractures, falls, myocardial infarction.[8] Opioids were also associated with increased risk for discontinuation because of gastrointestinal adverse events, somnolence, dizziness, and pruritus.[8]

The guideline recommends non-opioid therapies for the management of chronic pain (e.g. nonsteroidal anti-inflammatory drugs [NSAIDs] and acetaminophen), which should be prescribed for the shortest duration and lowest effective dose due to risk of adverse effects.[8] Furthermore, physicians should maximise the use of evidence-based, non-pharmacologic interventions.[8]

These interventions have been shown to improve chronic pain, as well as function, and are not associated with serious harms. Furthermore, benefits are sustained after completing treatment.[8]

Neuromodulation in the management of chronic pain

Neuromodulation, defined as "the alteration of nerve activity through targeted delivery of a stimulus, such as electrical stimulation or chemical agents, to specific neurological sites in the body",[9] is a non-pharmacological intervention that is increasingly being recognised as an alternative to pharmacotherapy in the management of chronic pain.[9]

To achieve targeted neuromodulation, electroceuticals have been developed that incorporate electrical, magnetic, optical, and ultrasound to control nervous system activity.[10] Chronic pain is associated with disease-specific alterations in the peripheral nervous system and central nervous system (CNS).[4]

One such electroceutical is pulsed shortwave therapy (PSWT), which has been shown to reduce chronic pain and improve QoL in several chronic pain conditions over treatment periods ranging from seven to 28 days.[10]

In 2017 the American Food and Drug Administration (FDA) approved ActiPatch®, a low-power PSWT device for the management of chronic pain associated with certain medical conditions.[11]

In 2020, a wearable version of ActiPatch®, which is available at local pharmacies, was approved by the FDA as adjunctive treatment for musculoskeletal pain.[12]

The good news is that the device is now available in South Africa. ActiPatch® is registered as a device under the Medicines and Related Substances Act 101 of 1965, as amended.

"Adcock Ingram is proud to bring ActiPatch® to South Africa," says Garth Maart, marketing manager, OTC division for Adcock Ingram South Africa, the company licensed to distribute the device locally. "We have no doubt that it can help provide chronic pain sufferers a new lease on life," he adds.

How does ActiPatch® work?

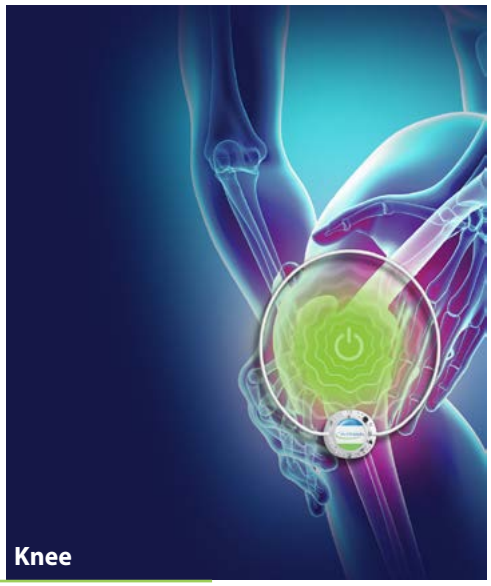
ActiPatch® is easy to use and does not produce heat or any sensation.[13] It emits a therapeutic radiofrequency field,[14] which stimulates neuromodulation of afferent nerves (nerves that carry signals toward the CNS from the periphery), dampening the brain's perception of pain.[14]

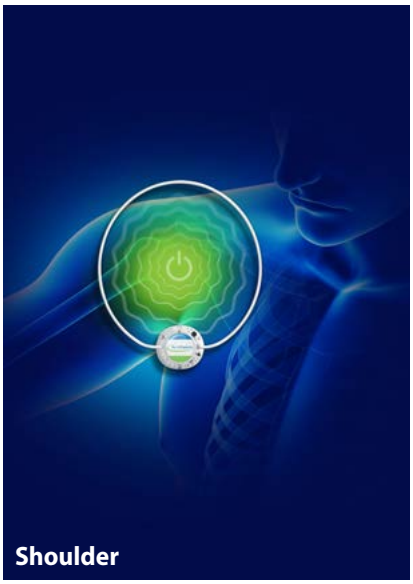
The device operates at 27.12 MHz, emitting pulses at a rate of 1000 pulses per second, each sustained for a 100 µs.[13] The peak power is 73 µWatts/cm^2 with an electromagnetic flux density of 30 µT.[13]

Treatment is confined to the area within the 11.5 cm diameter loop antenna covering an area of 100 cm^2. The antennae is circular, soft and flexible and can be shaped to fit the area/location being treated as required.[13]

Another key component of the device is its three Volt battery,[14] which can last for up to 720 hours.[14] ActiPatch® can be used continuously for 24 hours per day and more than one device can be worn as long as they do not overlap.[14]

Images demonstrating device activated





ActiPatch®

PROVEN PAIN RELIEF[1-6]

ACTIPATCH® PROVIDES LASTING PAIN RELIEF*[1-6]

Musculoskeletal pain[1]

Osteoarthritis[1-4]

Rheumatoid arthritis[1,2]

Low back pain[5]

Fibromyalgia[1,2]

Sports injuries[1,2]

Tendonitis[1,2]

Plantar fasciitis[6]

*of pain symptoms associated with the conditions listed.

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adcock ingram otc

The device is switched on via an on/off switch and can be affixed over the target area of the body using either medical tape or a specifically designed wrap.[13]

Efficacy and safety of ActiPatch®

The efficacy of ActiPatch® has been shown in numerous studies.[13,15,16] Rawe et al. showed an average 50% reduction in medication use – including prescription drugs.[13] Back, knee, neck, shoulder, and hip pain was reduced by 56%, 59%, 53%, 57% and 58%, respectively.[13]

In terms of safety, ActiPatch® should not be used by women who are pregnant or think they may be pregnant as no studies have been conducted in this patient population. It should be noted that the device is not sterile, and therefore it is important to place it over a sterile dressing following surgery or in the presence of other wounds. ActiPatch® should not be used by skeletally immature persons (< 17-years) or to treat cancer-related pain.[17]

ActiPatch® benefits in a nutshell

The ActiPatch® device[14]

- Provides consistent pain relief for up to 720 hours.
- Can be continuously used for 24 hours.
- Decreases local pain sensitivity of the affected region due to an anti-inflammatory effect.
- Decreases central pain perception by a neuromodulation effect.
- Is available in a non-drug analgesic modality, which provides statistically significant and clinically meaningful pain relief.
- Is safe to use due to its novel low power mechanism of action.
- Reduces the need for analgesics drug, thus lowering the risk of adverse effects.

- Offers an alternative to analgesics for patients who are intolerant or unwilling to use pharmacotherapy.
- Reduces the potential for harmful drug-drug interactions.
- Is easy to use and cost effective.
- Reduces the need for advanced pain interventions.

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Relationships between health professionals and the pharmaceutical industry: achieving a balance

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Abstract

Health professionals and the pharmaceutical and medical-device industry have had a long and often problematic relationship. The interaction between for-profit companies trying to promote and market their products and the prescribers of those products has come under increasing scrutiny. Most of the current regulation is from the industry's side; health professionals and professional medical associations are taking much longer to disentangle themselves from this often unethical relationship.

Keywords: health professionals, pharmaceutical industry, conflict of interest, professional medical associations

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Read the full article online at http://www.sapj.co.za/

SAAHIP 66th Annual General Meeting and 36th Annual Conference 2023

The Southern Gauteng branch was given the task of organising the first face-to-face conference since the onset of the COVID-19 pandemic. It was decided that we needed to go back to our favourite venue, Champagne Sports Resort in the Drakensberg.

The conference committee

Convener: Jacquie Fox

Academic coordinator: Liezl Nightingale

Accommodation & travel: Thanushya Pillaye

Administration & assistance: Rashmi Gosai & Bhadrasheila Valla

'Time to Thrive'

The theme for the conference asked all attendees to reflect on the pandemic and showcase their resilience through the trials and tribulations and, ultimately, how they triumphed through it all.

In true SAAHIP tradition, the attendees travelling from Gauteng had to show their resilience as they battled through the trial of the bus breaking down just as it was leaving Johannesburg. The attendees anxiously awaited a new bus, that arrived a few hours later and the attendees could resume their journey to Champagne Sports Resort.

With a slightly delayed start, the conference started with an amazing motivational talk by Vanessa Carter, a patient advocate all the way from the United Kingdom. Vanessa helped motivate attendees by showing her trials, tribulations and triumphs as she battled a resistant infection after a car accident and how she had managed to travel the world inspiring people to overcome their battles.

Academic programme

This year's poster, podium and case scenario presentations showed the diversity of the SAAHIP members. From management perspectives through to challenging the Department of Health with child friendly TB formulations, there was something for everyone.

During the programme, there were five posters, 16 podium and nine scenario presentations. There were also eight pearl presentations.

Guest speakers included Dr Ravinetto from Belgium, who gave insights into pharmacovigilance in Europe. Attendees also heard from SAHPRA about their med-safety application for easy recording of adverse events.

The Pharmacy Council Registrar, Vincent Tlala, joined in virtually to address the attendees and gave information on how Council is accommodating current BPharm graduates who are unable to find internship posts. He also touched on the current situation regarding specialisation.

Attendees listening to the academic programme

Northern Cape/Free State branch members attending the gala dinner

Joggie Hattingh, one of our past presidents and current PSSA president, also addressed the attendees.

Social programme

Fresenius Kabi sponsored the Thursday night dinner with the theme Superheroes, and brought in Nikki Bush, an author, speaker and facilitator, to help attendees learn how to reframe disruption. Nikki got everyone thinking about how each choice that is made is a disruption to people's lives and that people have the power to make this disruption a positive one. Nikki also got the juices flowing by facilitating team challenges.

On Friday afternoon, the branches were sent out onto the estate to find puzzle pieces using emojis as clues as to where they were hidden. The branches then had to assemble the puzzle. None of the branches managed to retrieve all the pieces, but KZN Inland was the first branch to find the most pieces.

Equity Pharmaceuticals brought us 'Bac' to the party on Friday evening. Before we were enthralled by the amazing father-daughter drumming duo, attendees had to show who had the fastest fingers on the night with an interactive quiz. It was every man for himself, with Doctor von Awesome showing everyone he had what it takes to get to the top of the leaderboard!

The gala dinner was sponsored by SAAHIP. Each branch was invited to decorate their tables with a unique and special touch to celebrate their triumphs through their trials and tribulations. In true 'wine route' fashion, Western Cape came out on top.

Trade representation

We were once again fortunate to have our industry partners attend our conference. Sixteen companies were in attendance in the exhibition hall, with another two companies sponsoring teas and breakfasts.

Trade sponsorship companies

Abbvie
Adcock Ingram Critical Care
Astra Zeneca
Aurogen
Bayer
Biovac
Bluesky Healthcare
Cipla
Equity Pharmaceuticals
Fresenius Kabi
National Bioproducts
Novartis
Novo Nordisk
Organon
Pharma Dynamics
SAHPRA
Sandoz
Sonke Pharmaceuticals

Conference awards

Mediclinic case scenario award

Winner: Nirupa Misra

Topic: We are the children – hear our voices – improving access to CFF

Life Healthcare best podium award

Winner: Ruth Lancaster

Topic: Superheroes with bionic vision: Monitoring medicine availability during the COVID-19 pandemic

Life Healthcare best poster award

Winner: Armand Algra

Topic: Thriving by education: Shining the light on handling light sensitive medication

Best academic presentation

Winner: Hazel Bradley

Topic: Developing training material for community health workers on adverse drug reaction reporting: A pilot project

Adcock Ingram pearl presentation

Winner: Thembelihle Siyaya

Topic: That lustful second glance

Membership award

KZN Inland branch

Spirit award

Limpopo branch

Best overall trade exhibition

Adcock Ingram

Most informative

National Bioproducts

Best hospitality

Equity Pharmaceuticals

Best appearance

Adcock Ingram

Newly elected Presidential Committee

President: Nhlanhla Mafarafara
Vice-President: Obey Madzingo
Secretary: Carrie de Beer
Treasurer: Danielle Tshabalala
Past President: Shawn Zeelie

The Southern Gauteng branch will be welcoming attendees to the next AGM and conference in 2025. SAAHIP has elected not to have a conference in 2024 due to the FIP conference being held in Cape Town in September 2024.

Newly elected Presidential Committee

Cum Laude

Academy of Pharmaceutical Sciences

Edutaining the 21st century

Ané Orchard

Corresponding author, email: ane.orchard@wits.ac.za

"Every student can learn, just not the same day or the same way"

George Evans

Ané is the winner of the 2022 Teacher of the Year award

 S Afr Pharm J 2023;90(3):43-46

Teaching is a profession of attending to the educational needs, experiences, and feelings of students. Education not only addresses the objective for a teacher to relay the didactic information but should also be an experience that considers the feelings of students.

Ané Orchard

Feelings and experiences are often overlooked in lecturing; however, it is a core aspect around which I centre my teaching. The experience of learning affects emotions, and emotions affect a student's willingness to engage, their cognitive development, and motivation toward education.[1,2] Anger, boredom, fear, and frustration are emotions that will have a negative effect on a student's learning experience, whereas positive emotions encourage self-regulation.[3]

As an edutainer (a combination of an educator and an entertainer), I adopt an educational approach that makes use of core operational and interpersonal skills that include communication, organisation, planning, and building authentic relationships based upon respect and personal responsibility. While employing sound academic principles, the view of an edutainer is that one should be fluid and adapt to current times and cultures. This change in culture means a change in methods of teaching to build a dynamic educational environment.[4] Being an edutainer provides an overall satisfying teaching and learning experience. Humour adds to a positive emotional response, and emotion and cognition are intertwined.[1,2] Emotions hold attention and increase memory, for example moments in life, childhood, and career. Positive emotions interest and motivate us; if students enjoy the positive experience, they are motivated to learn. To meet the educational needs and encourage positive emotion and experiences, I have adopted an edutaining interactive teaching and learning approach. We learn best by doing. Therefore, to get my students to do things via interactive learning sessions, I use various edutaining forms or tools for teaching, such as interactive facilitation, simulations, reflection, the SOLO taxonomy, humour, teamwork and fun, and constructive authenticity.

Interactive facilitation

In the year 2020, I completed a Postgraduate diploma in Health Sciences Education (PgDip HSE) at the University of the Witwatersrand. During this degree, we did a section on blended and online learning where we were introduced to readings that really brought home the concepts in education (Figure 1). For successful distance learning, three types of interaction should be encouraged: student-content, student-student, and student-facilitator.[5] Additionally, the need for online lessons to be meaningful is emphasised.[6] These readings discussed distance and online learning, yet the lessons taken from them are relevant to all teaching. It made me think – any time that the student puts towards learning should be meaningful as time is valuable, why then teach in a manner that a student can do on their own? Why should that student come into class for that lesson? What makes it more meaningful than being done online? If the lesson is online, why should that lesson be online? What makes it more meaningful than being done in the classroom environment? How can we ensure that the way that the student's time is spent is the best way that will help a student grasp a concept? Didactic lectures, whether face-to-face or online, just didn't seem meaningful anymore. Moore[5] stated that interaction is so important. A didactic lecture delivers information, how much is grasped though? What if information is given in smaller chunks, followed by questions (content-content interaction), or a discussion (student-student interaction) and constructive feedback following a reflection

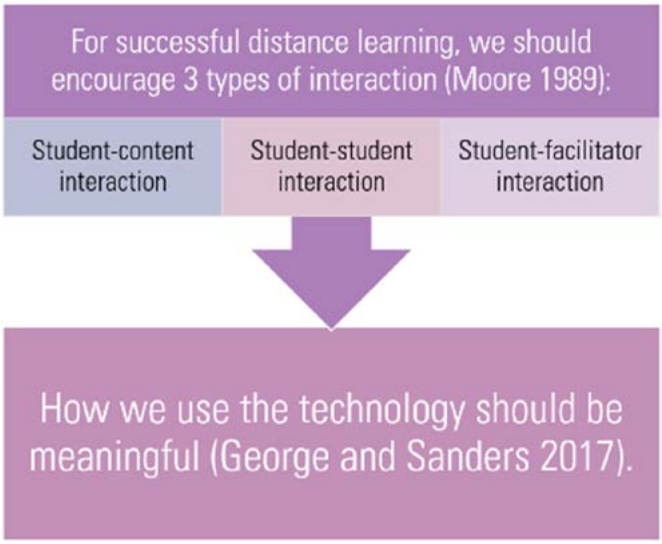

Figure 1: Focus points in designing lessons

(student-facilitator interaction)? Well, to answer that question, studies show enhanced cognitive learning.[7,8]

Simulations

These learning activities simulate, or allow for the imitation of, real-world processes using software, model patients, or computerised interactive manikins. Simulation allows us to expose students to various environments or situations that may not be easily or readily accessible due to them being rare or risky, however, are essential for students to construct their knowledge.[9,10] The simulations allow students to develop critical thinking in an intellectually stimulating environment as they are in situations where they need to solve problems. It also provides opportunities for students to transfer their theoretical knowledge into practice.[9,11] For my students, I make use of the Wits Simulation lab for them to practice several high-fidelity (full-scale computerised patient simulator) scenarios. The students are first given the pharmacy simulation activity case scenarios and objectives and are then required to prepare for the simulation. The simulation is performed by the students, and constructive feedback is provided afterwards by me. This is followed by the students having a group discussion session and debriefing, and finally, an individual student reflection needs to be submitted. The simulation lesson plan is designed in a way to encourage students to take responsibility for their own education.

Reflections

I confess, I did not really understand the point of reflection before completing the PgDip HSE. It is, however, now a learning tool I have come to greatly appreciate. When done appropriately and with adequate guidance, it helps students realise what they have learned and developed. Reflection helps students with practical knowledge, it helps them realise where their knowledge is

1	2	3	4	5	6	7
No evidence of affective learning	'Receiving'	'Responding'	'Valuing'	'Organisation'		'Characterisation'

Figure 2: Griffith University Affective Learning Scale[16]

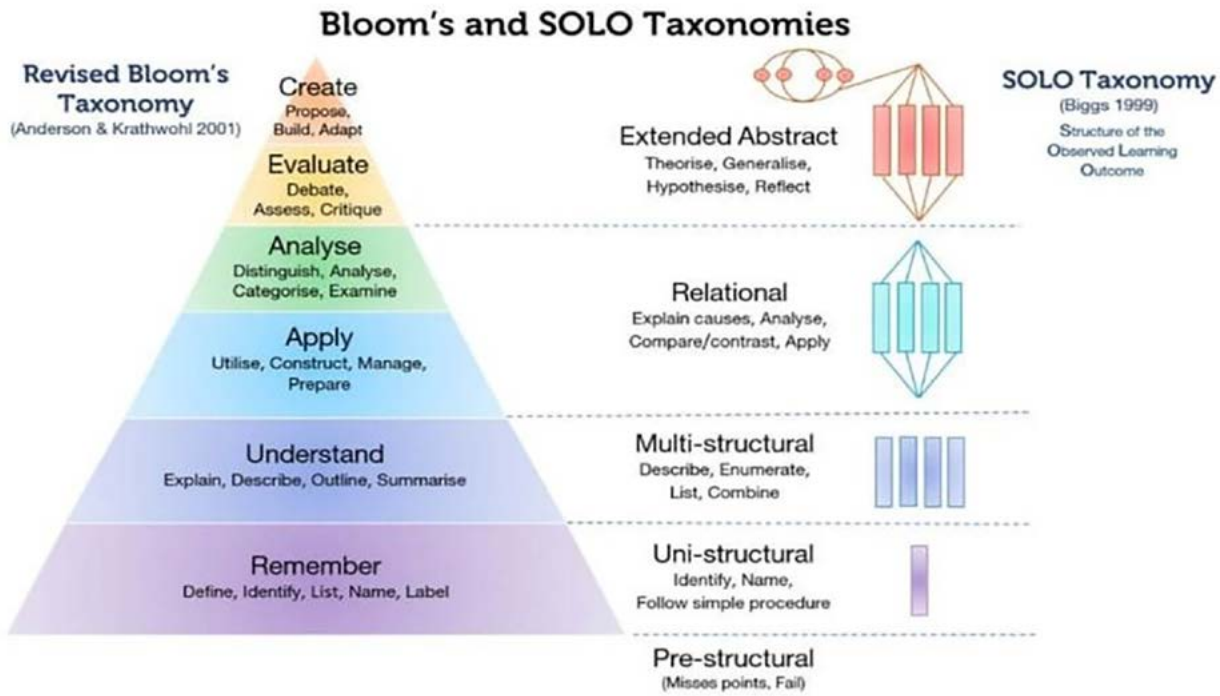

Figure 3: SOLO taxonomy[19]

inadequate, and encourages deeper learning approaches and self-regulation.[12-14] One of the key considerations I have learned with reflections is to guide students with prompting questions, provide them with constructive feedback, and inform students of the purpose of doing them. In general, for self-regulated learning, adults need to know the WHY, for example, WHY are they learning?[14] Since becoming aware of the importance of needing to let students know why they are doing a learning activity, I approach the task by providing context and relevance before teaching the concept. Reflections are marked using the validated Griffith University Affective Learning Scale (GUALS) tool for assessing affective learning in health professional students (Figure 2).[15,16]

Going SOLO

I make use of the Structure of the Observed Learning Outcome (SOLO) taxonomy (Figure 3) more often for student submissions, which I prefer over Bloom's taxonomy. The SOLO taxonomy evaluates the quality of learning and is based on levels of ascending cognitive complexity. It is beneficial when giving students feedback and has high inter-rater reliability (consistency between different judges).[17,18] Since introducing the SOLO taxonomy, I am able to articulate feedback more constructively as I better identify where the student needs guidance.

The humerus lessons (get it?)

I noticed that once students develop a dislike for a subject/theme/system, it instils dislike or fear and unwillingness in them. What better way to overcome this than humour? For "difficult" sections, I would often do an "ice breaker" to take away the intimidation that students feel towards the section, to help them realise it is doable after all. From what I have observed, students are often overwhelmed by all the pharmacology they need to know, so I use mnemonics and descriptive wording to thus help students remember. E.g., *I MET a guy because of METformin. Why? Because it can cause weight loss!!! Lispro is fast acting, cause when I am "lis" for something I want it fast!*

Teamwork and fun activities

Gamification of education is an area that is receiving more and more attention due to its benefits of active learning in helping students transition from memorisation to more meaningful

learning.[20] Gamification is a creative solution that has the potential to be a high-quality, useful, fun and cost-effective educational tool all over the world.[21-23] I use the concept of the Amazing Race to create a new fun, competitive environment for my students to revise their knowledge/skills, which we call 'The Amazing Pharmacist'.

This has been implemented for three years. The first year (2017) was based on antibiotics, incorporating all the final-year pharmacy subjects. In 2019, the Amazing Pharmacist Race was used as a revision tool for student screening skills. In 2022, the race was designed around an integrated cardiovascular system revision session. This afforded both students and facilitators a unique experience and entertainment, more importantly, facilitators were able to identify which areas students were struggling with most. Once identified, it provides an opportunity to provide focused revision before the summative tests.

Constructively authentic

My teaching philosophy is centred around constructively preparing students for practice after graduation. I aim to equip students with the ability to apply their knowledge, not just making sure they become carriers of information. They must know how to use their knowledge and I am here to guide them on how to think, not to tell them what to think.

To encourage this kind of development, my teaching focuses on strengthening the core knowledge of students with interactions that includes outside-the-classroom practices such as seen with a screening programme called STEPPS, under the supervision of the clinical pharmacy lecturers. The Screening and Testing Programme by Pharmacy Students (STEPPS) allows students to interact with patients and practice what was learned in the classroom, which also contributes to boosting the confidence of students.

In STEPPS, we train third- and fourth-year pharmacy students in various techniques offered in a pharmacy. These skills include, however, is not limited to the following:

- Anthropometric measurements and obesity
- Hypertension
- Cholesterol
- Glucose, HbA1C, and diabetic foot examinations
- Atrial fibrillation detection via a single lead ECG
- Urine analysis
- Injection techniques
- Asthma inhalers and peak flow
- Haemoglobin
- HIV screening
- Mini-mental health examination

The students receive training via background lessons, then practice sessions and a revision session.

The STEPPS programme also allows for exposure and involvement in May Measurement Month (MMM). This is a global initiative that aims to screen as many people's blood pressure during the month of May, bringing awareness to hypertension (high blood pressure), and to identify as many people with high blood pressure as possible. In 2022, the University of the Witwatersrand Clinical Pharmacy team and the Pharmacy students that participated screened 1 218 participants, making us the largest contributor to South African MMM stats. Exposure of STEPPS and MMM allows students to be proactive in their social responsibility and also allows ideal opportunities for my students to transfer their theoretical knowledge into practice. It has been very well received by our students.

Student (2019) testimonial:

"*It was the best thing I did in my four years of studying.*"

All in all, teaching is a passion and I find it best achieved using different edutaining activities, tools and approaches. Using a variety of interactive teaching methods and focusing on constructive feedback and fun experiences allows for different ways in which students learn in an authentic and positive environment while keeping them engaged and guiding them in becoming conscious of what they can offer the world as a pharmacist. It is such a unique opportunity to help shape the future-ready 21st-century pharmacists.

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Pharmaceutical Practitioner
South African Association of Community Pharmacists

Faxed and emailed prescriptions – the dilemma with S5 and S6 medicines

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Pharmacists are often faced with an ethical and a legal conundrum when presented with requests for scheduled medicines with or without a written prescription. This article will focus on the regulations for Schedule 5 and Schedule 6 prescriptions.

Legislation review of the Medicines Act

Section 22(A)(5)b of the Medicines and Related Substances Act (Medicines Act) clearly explains that in terms of verbal prescriptions *(5) Any Schedule 2, Schedule 3, Schedule 4, Schedule 5 or Schedule 6 substance shall not be sold by any person other than—*

(b) a pharmacist or a pharmacist intern or pharmacist's assistant acting under the personal supervision of a pharmacist, upon a written prescription issued by an authorised prescriber or on the verbal instructions of an authorised prescriber who is known to such pharmacist;

From the same legislation, Section 22(A)(6)b states that:

(6) Any sale under subsection (5) shall only take place on condition that—

(b) the authorised prescriber who has given verbal instructions to a pharmacist to dispense a prescription shall within seven days after giving such instructions furnish such pharmacist with a prescription confirming such instructions;

In the latter scenario, in the case of verbal instructions the treatment period shall not exceed seven days.

Changes in the General Regulations to the Medicines Act (Act 101 of 1965)

Regulation 33(3) clearly states all the requirements for a prescription to be deemed legal. This includes aspects such as the details of the prescriber and the patient, information on the medicine prescribed, the dose, strength, duration of treatment and number of repeats.

When you receive a prescription, whether a hand written copy or via fax, email or WhatsApp, they mostly fulfil these requirements. So as far as the legality of the prescription is concerned, the prescription is deemed to be a legal prescription.

The new regulation, Regulation 33, formerly covered in Regulation 28, clearly omits the words "Faxed or Electronic prescriptions" and relates only to verbal prescriptions that need to be followed up with an original prescription, as the following extract shows:

(5) In the event of a prescription transmitted electronically by means other than an electronic agent in terms of subregulation (1), by fax or communicated verbally, a permanent copy of the prescription shall be made for record purposes.

(6) A verbal prescription shall be followed by the signed prescription as per sub regulation (2) within seven working days from the communication.

With the changes in the General Regulations in 2017, whether intentionally or unintentionally, the requirement to follow-up faxed or emailed prescriptions with the original prescription within seven working days of such communication, was omitted. This leaves a potential gap for medication abuse and overuse, as these prescriptions can be submitted to several pharmacies for dispensing. This makes it very difficult for pharmacists to verify the authenticity of the prescription and the intention of the treatment if it cannot be guaranteed that the same prescription has not been dispensed somewhere else as well.

How can pharmacists responsibly manage this gap in legislation and what can be done to support them in this dilemma?

Potentially, there has been an omission with regards to the wording in the regulations with reference to faxed, emailed, or social media transfers of prescriptions (either WhatsApp, Instagram or others). What we need to ask ourselves is: was this a genuine omission or was it an intentional omission?

If it was intentional, what was the objective for omitting faxed and emailed prescriptions?

If it was intended to make the patient's need easier to fulfil, then the pharmacist now has the added responsibility of ensuring that the request is a genuine one and that the prescriber has genuinely sent that prescription to the patient. Or has it been sourced from any other of the patient's providers? What about a picture of the prescription on the patient's mobile telephone? Quite clearly this type of transfer of a prescription can lead to overuse and abuse. Many patients ask if they may take a photo of the prescription *"to keep for my records"*. This can quite easily be done before the patient arrives in the pharmacy and then presents the photographed prescription when attempting to fill it at another pharmacy.

If it was an intentional omission, would this place the pharmacist in the invidious position of having to comply with the rule?

Clearly a pharmacist will only dispense Schedule 3 and higher scheduled medicines on a prescription that, in the opinion of the pharmacist, is genuine and valid and meets all the requirements as prescribed in the regulations of the Medicines and Related Substance Act (Act 101 of 1965).

Regulation 33(4) requires that the pharmacist who dispenses such a prescription shall verify the authenticity of the prescription before dispensing it.

The onus on the pharmacist to ensure and comply with all the regulations becomes difficult in the course of performing his duties and complying with the rules and regulations.

In many instances, pharmacists are confronted with some or all of the following situations:

- Out-of-town patients with an original prescription with trailer labels stuck all over it. The patient insists that they are on holiday and are going to run out of their medicines and will be returning home in two- or three-days' time.
- Patients paying cash for medicines – this transaction is not going through a medical aid and therefore a similar claim that could have been made recently cannot be detected.
- Telephone call by the prescriber's rooms. The patient insists that they can forward the email to the pharmacy right away. The patient insists that they cannot do without the medicines.
- An authorised prescriber known to the pharmacist faxes or transmits electronically (by email) a prescription to the pharmacy which clearly is missing all or some of the statutory requirements required to be in the doctor's handwriting, e.g., name and address of the patient, quantity of the prescribed medicine, proper dosage, qualifications, etc.
- A prescription has expired, i.e., beyond the six-calendar month limit and the patient requests an emergency supply until he/she is able to renew the prescription from the authorised prescriber.
- There are a host of other instances where very often the patient is trying to obtain medicines without a valid prescription. Many examples can be listed: the number of times medicines fall into toilets or are eaten up by pets, justifying another supply of medicine earlier than anticipated, are some of the reasons given by patients.

Furthermore, there seem to be discrepancies between the two health care councils, the Health Professions Council of South Africa (HPCSA) and the South African Pharmacy Council (SAPC). In the HPCSA's ethical guidelines for healthcare professions, the following ethical principles were found:

For S1 to S4, prescribers may issue typewritten, handwritten, computer-generated, pre-typed, pre-printed or standardised prescriptions. However, for S5 to S8, prescribers may only issue handwritten prescriptions.

In other words, dispensers should actually only accept handwritten prescriptions for S5 and S6 because there may not be any other form of prescription in circulation for S5 and S6 medicines.

Keep in mind that this legislation is for professionals registered with HPCSA, and currently there is no legislation on the side of pharmacy, e.g. in the Good Pharmacy Practice (GPP) that forbids the dispensing of computer-generated prescriptions for S5 and S6.

Pharmacist's responsibility

As pharmacists, it is the responsibility of the profession to ensure that all prescriptions issued by an authorised prescriber comply with the above minimum requirements. Too often a pharmacist may feel threatened or face abuse if he/she requests that the prescriber complies with the minimum requirements that should be on the prescription as stated above. It is common practice when dispensing a Schedule 6 medication that most pharmacists will request that the required details appear on the prescription. Some may ask the patient to return to the prescriber to have the prescription completed correctly so as to comply and be in agreement with the regulations so as to comply with the minimum requirements.

I am sure that the ongoing education of the prescribing practitioner will in many cases alleviate the problem so as to have prescribers comply with the minimum requirements and particulars. Who should perform this education process going forward? A number of pharmacy professionals in the ranks of the SAPC are well qualified to perform such education. Yes, it may be a long, slow and laborious process, but who is best qualified to present the dilemma faced by pharmacists other than a pharmacist?

Lectures, seminars and presentations in the early years of training of medical doctors would go a long way in advising and enlightening medical practitioners of the minimum and statutory requirements necessary for the valid issuing of prescriptions, especially pertaining to all the schedules and not particularly Schedule 6 prescriptions.

Another option may be an information pamphlet sent to all authorised prescribers detailing the requirements as per the regulations.

Further, as an interim measure, the possibility of printing of a computer-generated address label by the dispensing pharmacist can be done. This is then attached to the prescription by the pharmacist.

Shared responsibility

The question is: should these compliance details be the sole responsibility of the pharmacist, or is this a shared responsibility? In my opinion, there needs to be a shared responsibility by both prescriber and pharmacist and the legislative authority collaborating to ensure that the best treatment for the patient is given and that the patient receives the best and most efficient service at the point of collection of his/her prescription.

Pharma Dynamics launches Rubaz – a new combo contraceptive

Leading generics provider, Pharma Dynamics, continues to empower women with the launch of Rubaz – a new cost-effective combination oral contraceptive (COC), which is now available on prescription.

Rubaz combines oestrogen (ethinylestradiol 0.02 mg) and progestin (drospirenone 3 mg), which is used as a birth control pill to prevent pregnancy in women with the added benefit of treating acne, and the symptoms of premenstrual dysphoric disorder (PMDD).

Studies show that taking ethinylestradiol and drospirenone regulates periods, decreases blood loss, eases pain, while also decreasing the risk of ovarian cysts.

René Schickerling, women's health portfolio manager for Pharma Dynamics says the pill is by far still the most prescribed oral contraceptive in the world. "Women describe it as easy to use, convenient and discreet. It's also 99% failure-proof when used correctly."

"Another benefit of using Rubaz is its effect on acne. Acne mostly affects the face and can result in a substantial psychosocial burden – especially for women, leading to low self-esteem, social isolation and poor body image. Drospirenone in Rubaz has an anti-androgenic activity, which helps to clear moderate acne vulgaris."

Rubaz has been shown to be bioequivalent to the originator and is therefore therapeutically interchangeable with it.

Each pack contains 28 tablets of which one should be taken daily at about the same time every day. Once the pack is finished, a new pack should be started without interruption.

As part of Pharma Dynamics' ongoing strategy to support patients through health education, they have created a hub especially for women, which contains trusted and relevant content regarding reproductive health, which can be accessed here: https://www.mydynamics.co.za/condition/womens-health/.

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