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

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SAPJ Author Guidelines

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

Aims, scope and review policy

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

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

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

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

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

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

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2. This work is original and all third party contributions (images, ideas and results) have been duly attributed to the originator(s).
3. Permission to publish licensed material (tables, figures, graphs) has been obtained and the letter of approval and proof of payment for royalties have been submitted as supplementary files.
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6. Ethics committee approval has been obtained for original studies and is clearly stated in the methodology.
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Article sections and length

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

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

A Final Piece of my Mind

Editorial Comment

So long, and thanks for all the fish

You may, or may not (unlikely), know that I don't do schmaltz. (I definitely do not do the music of my parents' generation.) But I am faced with a situation that I knew would arrive sooner or later – it's time for me to take my leave as editor of the *SA Pharmaceutical Journal* and of the *Pharmacist's Assistant*. And suddenly I discover that I'm overwhelmed by memories and emotions, and, as you know, I find it impossible not to share my thoughts with you.

It's also impossible to look back on my time with the *SAPJ* without looking back at other aspects of my life – how on earth did I arrive at the *SAPJ*? Just as Sham Moodley shared with us a while ago that he was an accidental pharmacist, I was not only an accidental pharmacist but also an accidental editor.

How did it begin?

It probably goes back to my pre-school days. I learnt to read sitting on my father's knee. Actually, I learnt to read the newspaper, which could explain my interest in politics, including pharmacy politics. I didn't enjoy sports at school (I might have, had they offered snooker as a sport – after all, it's all about vectors) but I did enjoy the drama club and the debating society!

Joining the working world

My working life began in a medical microbiology laboratory, working during the day and attending lectures in the evening.

I loved it, but eventually family life became more important – I married, and had two daughters. I still worked part-time, but clearly not with the same enthusiasm! When my mother decided to buy a florist shop, I trained as a florist and worked with my mom.

The life-changing decision!

At the grand old age of 26, I decided that I needed a real career, so I enrolled to study pharmacy. My life changed forever. In my first year of study, I fell in love with organic chemistry – it was the most amazing fairy tale I'd ever heard. I wasn't convinced that any of it was actually true. When I heard that electrons need not necessarily be in the same room as their protons, it conjured up the most beautiful pictures of electrons flitting about like the fairies that little girls dream about. Or perhaps they were more like bees. I'm still sorry I didn't spend more time on it! Please don't disillusion me by pointing out the reality!

While a student, I worked part-time, not in a pharmacy, but in the microbiology laboratory. There was a simple reason for this – I was paid much more than I would have been paid in a pharmacy! But then, I was much more useful in the lab than I would have been in the pharmacy.

Student politics

I became involved in student politics, first as secretary of what was then the Witwatersrand Pharmaceutical Students Association, then as secretary of the South African Pharmaceutical Students Federation. Then came something that hinted at my future involvement in the *SAPJ* – I became the Chairman of Publications of the International Pharmaceutical Students Federation.

Internship

My internship was in a community pharmacy and I learned a lot, not just about dispensing and medicines, but about people. The very first task I was given was to phone a medical scheme administrator to complain about the rejection of a claim. I must say that, although I later discovered that I much preferred working in a hospital pharmacy, the interaction with people was invaluable.

It is such a pity that not all pharmacists have that opportunity during their formative years, whether they intend to work in community pharmacy or not. It is definitely useful for learning how to keep your cool when confronted (literally) with different personality types and different communication skills. Whichever career path you choose, the skills you develop under these circumstances can only benefit you.

Experiencing academia

The next phase of my career was completely accidental. In the last month of my internship, I received a phone call to say that the Microbiology lecturer had resigned, and I was asked if I wanted the job. (You don't get offered a job in that way any longer – that was in the olden days!) I had nothing better to do, so I accepted, and thus began the next leg of my journey. Somehow Aseptic Technology was added to the mix when that lecturer left abruptly.

After a while, I changed subjects. I switched to Pharmacy Administration (having had practical experience in both the florist shop and a community pharmacy in which I had a partnership) and became involved in Forensic Pharmacy, where I found my niche.

Locums in hospital pharmacy

Although I had grown a lot and learned a lot in community pharmacy, when my partner and I sold the community pharmacy, I decided that I wouldn't work in a community pharmacy again, and I kept my promise. I started doing locums in private hospitals, and continued to do so for the next twenty years. It was certainly very satisfying to engage in discussions (sometimes a.k.a. disagreements) with doctors and nurses, rather than with patients – they were far more likely to succumb to facts and logic than patients, who tended to react more emotionally.

Dabbling in product registration

When I left the university, I worked in product registration for an animal health product manufacturer. I thought that my enjoyment of legislation would mean that I'd enjoy the work. I was wrong. This was before electronic submissions to the then Medicines Control Council, and I really wasn't suited to sitting in a room surrounded by piles of files containing tons of paper.

The posters surrounding me didn't help – I grew really fond of pigs, and extremely concerned about baby chicks.

The PSSA to the rescue

Having been very involved in student pharmacy politics, it was natural to join the PSSA. At some stage, I was a member of the National Executive Committee. In those days, Exco members were given a portfolio. Mine was the *SAPJ*, so I learned a lot about the *SAPJ* and how it worked. I attended editorial meetings, and I watched as the staff literally "cut and pasted" the layout of the pages.

I even applied for a job at the PSSA, but was told by the Executive Director at the time that the job wasn't suitable for me – it involved driving around at night and he wouldn't want his daughter to drive alone at night! (And I swallowed it! Those were the days!) Luckily the current Executive Director didn't share his views, and when a vacancy occurred later, he was brave enough to employ me! (He didn't know what he was letting himself in for!)

The Great Trek

At first, I was involved in book sales and arranging CPD lectures, but then the PSSA National Office had its own Great Trek – we moved from Johannesburg to Pretoria. It made perfect sense. The SA Pharmacy Council and the National Department of Health, as well as other official role players, were all in Pretoria, and four of us from the National Office made weekly trips to Pretoria.

When we moved to Pretoria, the Editor of the *SAPJ* at the time decided that it was too far for him to travel daily so he resigned. (He subsequently moved to Scotland.) We had a mini-crisis – what to do with the SAPJ? Having been the Exco member to whom the *SAPJ* was assigned, I volunteered to step in until a real editor could be found.

That was 25 years ago. I couldn't believe it until Ivan pointed it out to me. Twenty-five years!!!! That's a really long time to have a babysitter!

My years with the *SAPJ*

What can I say? Let's get the negatives out of the way first! Mainly because they're relatively minor, easily solved. The major one is that I'm easily distracted – if something more interesting comes along, and I'm supposed to do something boring, I'm out of here. So what's boring about the *SAPJ*? Proofreading, mainly. Sticking to deadlines, too. Luckily, there's been a wonderful solution to both of these for many years. Her name is Nitsa Manolis. Thank goodness for Nitsa. She is a former medical lab technologist, so she knows about deadlines and organisation and precision, and she applies them all strictly, but oh so gently. When she started working at the PSSA, she quietly went and earned a second B.Tech. in her spare time, this one in Pharmaceutical Sciences, so that she'd understand the world she was entering. If it weren't for Nitsa, there would be no *SAPJ*! Thank you, dearest Nitsa, for always being by my side, and helping me to overcome my natural procrastination. And thank you for the sterling work you've always done.

I can honestly say that I've never been bored in my work – how many people can say that!

Thanks to the PSSA

Thank you to my friends at the PSSA for always being there for me – there was always someone to lend a hand or an ear, whichever was needed. Thank you to Tersea, Dinette, Nikita, Sinah and Peter – the office runs smoothly because of you. Michelle, I didn't have the pleasure of working with you, but I'm sure you've had the same experience.

Our professional staff, Mariet, Anri and Nitsa, you are all stars. Ivan, I'll cry if I start saying how much you've meant in my journey through the PSSA. You've been a mentor and eventually, it's now time that I can introduce you as my friend, rather than as my boss. You've always been there to advise and support me, and to help me to explore my potential and use skills that I didn't know I had. Thank you.

And now, it's time to hand over to my successor. And what a successor she is! I can't tell you how happy I am that it is Natalie Schellack! Natalie has her own story to tell about her journey to the *SAPJ*, and I won't spoil it – it's her story – but I will say that I know that she's going to be both happy and productive in her new role. And, Natalie, have some fun along the way!

Two aspects of my employment at the PSSA had nothing to do with the SAPJ, but I appreciated the trust that Ivan and the Presidents at the time put in me.

In the early 1990s, thanks to Medpharm, I hosted a weekly TV programme for pharmacists. We were perhaps a little ahead of our time – relatively few pharmacists had DSTV and it was before podcasts became popular. It was a lot of work, but great fun, and of course I insisted on learning how to do video editing! The biggest challenge? To make sure that someone's mouth was closed when you stopped their speech!

The time that I was most aware of my responsibility, because of the trust placed in me, was during the crisis when the dispensing fee was first introduced. As the PSSA spokesperson, I had to be alert all the time so that I could respond appropriately to whatever was said, whether it was by an enquiring journalist or an antagonistic official. Most interviews, whether radio or TV, were live, so there was no room for errors. Nerve-wracking, but what a relief when they were over! Thank you, Ivan, for believing in my ability to represent the PSSA adequately in that difficult situation.

During my time at the PSSA, I also appreciated the opportunity to be involved with the Commonwealth Pharmacists Association (CPA)

first as the PSSA representative but later also as the Southern and East African regional representative. It was also an honour to serve a two-year term as Vice President.

I am deeply humbled to have been recognised as a Fellow of both the PSSA and the CPA.

I was touched and blessed to receive honorary life membership of the Wits student body, which at the time was called the Witwatersrand Pharmaceutical Students Association, the South African Pharmaceutical Students Federation and, much later, the Academy of Pharmaceutical Sciences and the South African Association of Hospital and Institutional Pharmacists.

I was privileged to serve two terms on Pharmacy Council, at various times serving on the Committees for Preliminary Investigation, Continuing Professional Development (as chair), Practice, Audit and Formal Inquiry (as chair). During my second term of office, I served as Vice President. Thank you to Ivan for his patience during this time, it showed not only my commitment to the profession, but also his.

Farewell to our readers

Thank you for all your support over the years. It kept me going. And how lucky am I? I'm leaving now, knowing that we've shared so much of ourselves in these pages. The heartbreaking and painful times, the serious moments, the funny episodes. Thank you.

Go well, and God bless.

PS – What do the fish have to do with it? "So long, and thanks for all the fish," was the message left by the dolphins for the humans when the dolphins finally left the earth, in the Hitchhiker's Guide to the Galaxy by Douglas Adams. He was also the one who said, "I love deadlines. I love the sound they make as they go wooshing by." I couldn't agree more!

Lorraine Osman

President's Message

Do pharmacies and pharmacists really matter?

Joggie Hattingh
PSSA President

What a privilege it was to attend the FIP Conference after a two-year virtual-only interaction with fellow pharmacists from across the world.

Looking back at the pandemic and what has ensued, the question arises: What is the relevance of pharmacy in the world today?

To answer this question, we need to look at the world we are in and what it looks like. It is full of international conflict and crises. The nature of, and location of conflict changes continually, as does that of the international and local crises, but it is ever present!

For instance, the following report was released recently regarding COVID-19 regulations in China:

"*Authorities in Zhengzhou have announced a five-day lockdown including mass testing in eight of its districts, the latest city to revive daily tests for millions of people. Its 6.6 million residents have been told to stay at home, except to buy food and medicine.*"[1]

So, whatever businesses are closed, food and medicines need to remain accessible!

The war in Ukraine is another great example. I'm not going to get entangled in the politics behind it. I will simply discuss the role and relevance of pharmacy in the war.

As the war progressed, Ukraine started running out of medicines. Transport of medicines across the conflict areas was almost impossible as the vehicles were attacked, looted or destroyed. Many pharmacies were completely destroyed, whilst some closed down because they could not access any stock to continue serving their patients. As always, there are those who stay open at risk of life to serve patients with whatever they have left, even if it is only health advice.

How did the Ukrainian government react and what value do they see in their pharmacy services?

As reported: "*Fears that Russia could knock out power stations and other facilities this winter have led Ukraine to turn to special "invincibility centres".*

Thousands of the centres will be set up across the country to provide citizens with electricity, heat, water, internet service, mobile phone connections ***and a pharmacy***.

The services will be provided free of charge and around the clock."[2]

This gives us insight to the significance that pharmacies have during a crisis and makes me reflect on the feedback that was given at the FIP Conference of how pharmacies functioned during the COVID-19 pandemic. From all around the world the same report was given: At the height of the pandemic, when doctors closed their practice doors for patients and would only consult with them via phone or electronic media, pharmacies stayed open and were often the first (if not only) point of contact for patients. This disregard for their own interest and often for that of loved ones, to serve their patients, was what was reported about pharmacists all over the world!

What are the lessons we have learned from the pandemic and from international conflicts and similar crises, especially in terms of medicine and medical consumables availability?

- Firstly, however well meant, DO NOT SEND physical goods. It takes up so much space, it is often not what is really required, and it takes so much manpower to manage.
- When it comes to medicines, medical consumables and equipment, it is totally unethical to send excess, unwanted or expired/soon-to-be-expired stock to those in crisis! It borders on a criminal action, even if it is well intended.
- The logistics in a crisis area are already challenging. How to sort out boxes of unused medicines, clothes, food, blankets, etc., becomes impossible and ties up the hands of those who are already under severe pressure.

Then how do we help?

- Firstly, communicate via official channels (not a call for donations on social media) and determine the actual needs.
- Secondly, make sure that any donations offered are in line with the needs and can actually be accepted. Legal requirements for medicines entering a country are not abandoned because there is a

crisis! It is actually more important to ensure that whatever medicine enters the country does not pose a health risk.

- Thirdly, and by far the best option, would be to support raising funds for the affected area. This way, they can bargain for best prices on the market. They can order the correct strength, dosage form and quantity. They can ensure quick clearance at their borders and effective delivery to the facilities that require these resources most urgently.

In summary, rather provide financial support, as unwanted "goods" may not meet the healthcare needs of those affected.

Please look at the guidelines that the WHO provided for the donation of medicines, medical consumables and equipment. These guidelines should form part of our own emergency plans.[3]

Interestingly, a very efficient fundraising campaign was done, using pharmacies amongst others, where a snap-scan was displayed on the pharmacy windows. No fear of corruption that the money must pass through hands, as the donated money goes directly to the beneficiary!

There is no way that pharmacy and all its sectors (hospital, community, academia and industry) can be ignored if South Africa want any chance to survive the next pandemic or whatever catastrophe! We are part of the solution and must make sure we are involved and included in the drafting of all disaster plans!

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Dispensing fee

The Minister of Health (MoH), on the recommendation of the Pricing Committee (PC), published the draft dispensing fee for pharmacists on 2 December 2022, and comments were to be submitted by 2 March 2023. At the date of writing, the Pharmacy Stakeholders Forum (PSF), of which the PSSA is a member, had not yet finalised the comments to be submitted.

Even though the draft fee was published too late in 2021 and 2022, it was encouraging to see it was a few months earlier than the previous years. However, it does mean the fee for implementation will only be published around mid-2023. From preliminary calculations the dispensing fee increase appears to be around 2.5%. This is disappointing as CPI in South Africa is around 7% and it would appear that the PC did not take CPI into consideration when calculating the dispensing fee. The same issue was seen with the SEP increase, as the PC allowed only a 3.28% increase. In comparison, the SAPC increased the annual fees by 6%, which is in line with CPI. The PSF will submit comments to the MoH and PC on the draft fee.

One of the main concerns of the PSSA surrounding the proposed National Health Insurance (NHI) is the calculations that the proposed Health Care Benefits Pricing Committee will use to determine reimbursement of services and medication costs if this is the experience over the last few years.

Labour law – essential services

An essential service is defined in Section 213 of the Labour Relations Act (Act 66 of 1995) (LRA). In terms of this Section, a service is deemed an essential service if it can be shown that the interruption of such a service would: "*endanger the life, personal safety or health of the whole or any part of the population*". Most current designated essential services are in the public sector, but there seems to be an increase in the private sector, often at the request of employers.

According to a CCMA list dated 2021,[1] the following public pharmaceutical services were previously designated as essential: pharmaceutical and dispensary as well as medicine quality and control laboratory supporting public sector medical, paramedical, nursing and emergency health services. In the private sector, pharmaceutical and dispensary services at private health or private health and welfare centres were designated as essential. At the same time, the manufacturing and supply of parenteral nutrition are essential services, irrespective of whether it is in the public or private sector.

On 18 November 2022, the Department of Employment and Labour published notice 1413 of 022 in Government Gazette No 47526. In the notice, the following services in the pharmaceutical industry are designated as essential:

a. the services of manufacture, supply and distribution of vaccines and or biologicals; anaesthetics; antiretrovirals to treat HIV virus; Immunosuppressants; Covid-19-related products; and antibiotics; and
b. the manufacture and supply of chronic medicines.

As well as the following services in the health industry:

a. The manufacture, supply and re-service of theatre drapes, and surgical gowns/ garments;
b. The manufacture of single use of theatre drapes, and surgical gowns/ garments.

It is noteworthy that similar to the manufacturing and supply of parenteral nutrition there is no distinction between whether these services are offered in the public or private sector.

According to a 2013 legal brief from Werksmans[2] the provisions of Section 74(1) of the LRA prevents employees working in a designated essential service from going on strike. The LRA does provide additional mechanisms to the employee. The employer in the essential service is restricted from utilising its own bargaining power to lock employees out of the workplace to compel them to accept the employer's terms and conditions. The LRA goes on to provide for a mechanism in terms of which essential service workers can legally and lawfully embark on strike action, provided that certain agreements are first put in place. Section 72 of the LRA allows parties in designated essential services to enter into a collective agreement, which can regulate the minimum services to be provided by workers in that essential service in the event of a strike.

This has the effect that the only employees who will be prevented from striking are the number of employees or a percentage of the workforce which is required to continue providing the minimum services. All other employees who are not required to provide the minimum service, even though they are employed in a sector or industry designated as an essential service, will be allowed to strike.

It remains important for members working in these services to be aware of this update and ensure they know their legal rights.

Pharmaceutical Community Service 2023

Over the years, community service has been associated with fear, uncertainty, misinformation, lack of communication, anxiety, stress, and frustrations. There are many reasons for this on the side of both the administrator of the system and the applicant. The PSSA found that sometimes applicants do not read instructions, do not provide accurate information, jump to unconfirmed conclusions, and are overall very emotional and impatient with preconceived ideas of a process they have never participated in before. As a result, the applicant then phones numerous times or logs multiple tickets, overburdening the system, which negatively impacts available time and capacity to manage the process. Data from the Internship and Community Service Programme (ICSP) found one person (not a pharmacist intern, though) who logged more than 100 tickets in three days. This action does not support the system.

Although the process management is out of our hands, the PSSA can support its members on how to best approach this process by providing them with clear, confirmed, directed information so that they can manage themselves accordingly.

The PSSA once again participated as an association stakeholder in the process of community service for the 2023 annual cycle. As early as August 2022, intern members of the PSSA were guided through a series of emails in preparation of the process for application and allocation. These communications included ensuring that contact information with the South African Pharmacy Council (SAPC) was correct and accurate since this information forms the basis of the ICSP system. This support is a PSSA member benefit, and interns should renew their membership to continue receiving the help.

Community service takes place over five phases:

- Phase 1: Verification of information on the ICSP system (or in the absence of, registration or updates to the ICSP system)
- Phase 2: Application for a post
- Phase 3: After allocation of posts, exchanges, and swop process (if necessary, not compulsory)
- Phase 4: Appeal process (if necessary, not mandatory)
- Phase 5: Finalisation of allocations and release of letters

For each phase, ICSP provided a guidance document accessible from its website. This information was made practical through pre-recorded presentations by the PSSA and the recording link shared with intern members at the appropriate time.

The verification process opened on Wednesday, 7 September 2022, and applications, which were due to open on 13 September, only opened on 21 September 2022 for pharmacists. The initial application closing date was 25 September, which was moved to 30 September and then again (on the PSSA's request) to 4 October 2022.

Several PSSA members had trouble verifying their initial accounts as their data was unavailable on the system. The reason for this is unclear, as ICSP received its information from the nine pharmacy schools and the SAPC. The PSSA reported these names (n = 131) to the ICSP daily during September 2022. This contributed to a delay in the commencement of phase 2 for pharmacists. The PSSA continued to assist members even after applications had closed (Phase 2). Other factors that contributed to the problems experienced by members were the (ongoing) electricity crises at the time, which impacted the staff's ability to perform their work during working hours. There were, on average more than 10 000 tickets pending.

From the first meeting, the PSSA realised, from the data and number of posts listed by the ICSP, that there would be a shortage of posts. It was sad to see that of the ± 2 010 bursary holders due to perform community service in 2023, only 38 (1.9%) were for pharmacy. Furthermore, provincial health departments pledged about 150 posts less than for the 2022 year, which meant that there could potentially be 220 posts short for 2023.

The National Department of Health (NDoH) has engaged with the private sector to offer posts for pharmaceutical community service to absorb this shortage, however it seems as if this request has negatively impacted the availability of internship posts, as a community service pharmacist may work without supervision. The private sector involvement in offering community service posts can also impact on the availability of post-community service posts.

During the application process, applicants had to submit supporting evidence for personal considerations, social compact, criminal records, or pending case or bursary obligations as part of the process, if applicable. These options did not guarantee preferential placements as the requested facilities' availability and the review panel's outcome influenced it.

Applicants had to select five facilities as part of the application. Priority was given to rural and underserviced facilities, as applicants had to apply for a minimum of three such facilities. An unambiguous directive was that commencement must be January 2023.

Although everyone had a similar opportunity to apply for a post during the 2023 annual cycle, allocations took place in a prioritisation fashion with the principal deciding factor being able to commence with community service on 1 January 2023. Citizens and permanent residents were placed first, and only then were foreigners placed. Applicants with successful personal considerations, social compact considerations, and bursary holders were placed accordingly. Interns who passed the August 2022 pre-registration examination, were competent in all six CPD entries, and interns who had completed their internship were allocated first. Following them were interns who had passed the August 2022 pre-registration examination but were not yet competent in their six CPD entries (prioritised from competence in five entries, then four and three entries).

Academic interns must await the outcome of examiners (not only submission) of their dissertations before their internship is considered to be completed and then they may commence with

community service. To manage this better, the ICSP reached out to all universities and asked supervisors to indicate the probability of academic interns receiving their results before the end of 2022. Pharmacy is the only health profession allowing internships in an academic environment. Some supervisors were optimistic that postgraduates would submit their dissertations in time, however this was not always possible and therefore incorrect information was given to the ICSP. This inaccuracy led to the allocation of academic interns to facilities that, due to their dissertation not being submitted, could not accept the post. These members will inform the PSSA once they have completed their internship. The PSSA will bring these names to the attention of the ICSP for immediate allocation, pending the availability of posts.

This year brought a unique challenge in that there were a number of interns that had not passed their pre-registration examinations during 2022 and will have to write in March 2023. This scenario was mainly due to not being competent in all six CPD entries by the ninth month of their internship (pre-requirement to write the October or subsequent examinations). These interns were not allocated to posts as they could not commence with community service as from January 2023. Currently, more than 100 interns have not yet completed their 2022 internship and, as a result, have not been allocated posts for community service.

This scenario will severely impact 2023 as there was a shortage of posts to start with, and the mid-year cycle is also known not to have sufficient posts to absorb all unallocated interns from the annual cycle process. The result will probably be an even more significant shortage of posts for the 2024 annual cycle when an increased number of interns will apply for community service later this year.

A unique appearance experienced this year for the first time is that of placed community service pharmacists who resign from their post within the first few days after commencement of duty. The PSSA is unclear whether this is due to interns having the wrong perception of what to expect from the community service year. Community service is precisely this – serving the community. Pharmacists who resign from posts will have to wait in line for a new allocation only after all other applicants in the system have been placed.

Part of the unallocated interns is those with foreign citizenship. Pharmacy is the profession with the highest number of foreign graduates applying for community service. The regulations on community service under the Pharmacy Act 53 of 1974 specify that all pharmacists must complete community service before they can be registered as pharmacists in South Africa. This requirement differs from, e.g. the same regulation under the Nursing Act 33 of 2005, only requesting citizens to perform community service. It is important to note that placement of foreigners in the community service process requires a request by the ICSP to the MoH, who will then liaise with the Minister of Foreign Affairs based on a policy that guides this process.

For this reason, it does not help foreigners at this stage to seek facilities willing to employ them and bring this to the attention of the ICSP. In principle, it is a high-level decision that will be made only once all citizens and permanent residents are placed. This decision is outside of the jurisdiction of the ICSP.

Any unplaced intern can practice the scope of practice of a pharmacist's assistant (post-basic) until they are allocated by the ICSP and can register as a community service pharmacist with the SAPC. Interns should apply accordingly.

Some points to consider by role players in the meantime are:

1. Interns must focus more on their internship requirements, especially CPD entries and exams. The SAPC offers workshops; these recordings are available on their website and social media platforms. Ensure you understand the requirements of a CPD entry. Don't just try to do it to get it over and done with, do it because it is a learning opportunity. Take guidance from the SAPC workshops, not your (uninformed) peer.
2. Interns need to take responsibility for their internship. Tutors should not engage with the SAPC or the PSSA on an intern's behalf. Tutors are there to guide, not to act as personal assistants.
3. Interns should be reminded of how to write formal professional communication. An email should not be confused with a chat platform where a one-liner response is the norm. Emails should be focused and to the point and should not be emotional. Be clear on what it is you ask or seek assistance for. Include all necessary details, such as your P-number and contact details.
4. Interns must ensure that their PSSA membership is updated from student members to interns to be included in communication regarding community service, which will commence around July 2023. It is also essential to update their indemnity insurance according to their revised scope of practice.
5. The purpose of community service is to place a person according to the need for healthcare services in under-serviced and under-resourced areas.
6. Interns must understand which parts of the community service application and allocation process can influence and which features they can't. Don't try to manipulate or change the programme's aspects that are not within your control, as it will only cause more frustration and anxiety. Rather know the information, consider it carefully, and then act accordingly. Don't make this harder for yourself than it already is. If you plan to get married or start a family, remember that the ICSP system will not necessarily cater to your circumstances.
7. Tutors must be aware of deadlines for submission of CPDs, monitor progress, and keep interns on track.
8. Academic interns should aim to submit their dissertations by the end of September to receive their results before the university closes for the festive season. Both academic interns and their supervisors (who are not necessarily the

tutor or a pharmacist) should understand that the university's submission date is only applicable to the institution and is not a guide for allocation in the community service process

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Young Pharmacist – The future is now!

"Bite off more than you can chew. Then chew it" – Ella Williams

It is not a secret that the economic climate of the country is rapidly changing. Although young pharmacists are fortunate enough to jump-start their careers, with at least two years of above market-related salaries for internship and community service. There is an impending looming crisis of unemployment that is facing us towards the end of our community service year. According to a 2022 Bain and company report*, younger workers have been exposed to a broader turbulence over the past decade, stating:

"The lives of younger generations are characterized by a far higher degree of ambiguity and uncertainty—and they simply haven't been educated on how to cope with it."

Further highlighting the economic challenges:

"Of all these issues, the economic stressors matter most to young workers." Over 60% of the respondents under 35 cited financial issues, job security, or failing to meet their career goals as their biggest concerns over the next 5 to 10 years.

There are many questions that the young professional is currently faced with:

"Will I find a permanent job after completing my community service?"

"Have I saved enough money to pay for that registration fee?"

"Am I even qualified enough to be in this space with all these experts in medicine?"

"Should I be studying further?"

"Is this what I want to do for the rest of my life?"

Social media also provides an added layer of anxiety as it never fails to show us how our peers in or out of the profession are succeeding, sometimes we see no resolution in sight.

However, underneath the gloom that young professionals are currently facing; here are a couple of things that we feel a young pharmacist should remember:

1. By virtue of the fact that we successfully completed the BPharm degree, we possess common qualities such as a strong sense of responsibility, attention to detail, resilience, leadership, high scientific knowledge, sensitivity, tactfulness, discretion, and adaptability. All these abovementioned factors place us in an ideal position to thrive in the uncertain and fast-paced developing world of healthcare.
2. We are extremely privileged to find ourselves in a dynamic profession that provides multiple avenues for growth, specialisation, and change that does not have only one ladder to reach.
3. It is our duty to remain informed about current national and international developments in the profession. Above that, we should also bring our voices to professional platforms, and nominate and elect not only those who have been in the seats for decades, but ourselves and our peers. Making sure we step up to the roles and demonstrate commitment to being the drivers of positive change.
4. We also need to keep our eyes on profession-adjacent developments and ensure that when matters are tabled about us, we are present, informed and ready to contribute to the resolutions.
5. Lastly, we need to be actively involved, consistently engage with one another, identify and approach potential mentors, ask questions, and create a community that inspires, motivates, and builds the profession that we are leading ***today***, not some far off day in the future.

Young pharmacists, this is our profession, let us not fall into the trap of being too busy to acquaint ourselves with the matters of the profession. It is our duty to actively look for gaps and find solutions to the doom that may be looming. Our time has been and is still now, we are the future and the future is now.

"I've learnt that you shouldn't go through life with a catcher's mitt. You need to be able to throw something back" – Maya Angelou

**Access the full Bain and Company article here: https://www.bain.com/contentassets/d620202718c146359acb05c02d9060db/bain-report_the-working-future.pdf*

The PSSA YPG gets involved with the FIP ECPG

The YPG would like to congratulate our Public Relations Officer, Ms Ntombizodwa Luwaca, for being elected to serve on FIP ECPG's Public Relations subcommittee as both the media coordinator and a support graphic designer. We believe that she will represent us well and bring new ideas that will contribute to the growth of this platform.

PSSA YPG Mentorship Programme Update

The YPG received 11 mentee applications towards the end of 2022 for the 2023 programme. We also released a mentor call in which we encourage all those who are eligible to apply and partake in the development of young pharmacists. The 2023 programme kicked off in early February with an orientation and leadership coaching session and more updates will be given in the following editions of the SAPJ. We are looking forward to welcoming a new cohort of mentees soon!

Professional Innovation Project (PIP) 2023 Call

The PIP 2023 submission cycle is currently open and we would like to invite you to apply. The goal of the PIP is to promote innovation in the profession of pharmacy and pharmaceutical sciences by supporting creative projects by young pharmacists (pharmacy practitioners and pharmaceutical sciences). This project should directly or indirectly benefit or improve health and demonstrate the value added by pharmacy to health. To find out more about this project and access the application forms visit the YPG's page on the PSSA website. The deadline to submit applications is 31 March 2023, we look forward to seeing your applications!

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!

Treating bacterial conjunctivitis – a bird's eye view

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Keywords: bacterial conjunctivitis, treatment, adverse effects

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Introduction

Conjunctivitis is a frequent presenting complaint to general practitioners and pharmacists. It may be further classified as either infectious or non-infectious in origin. Non-infectious causes include allergies and various irritants. Infectious causes may be further subdivided into bacterial and viral pathogens. Both forms are generally self-limiting.[1,2]

Causes of bacterial conjunctivitis

Gram-positive organisms are the main culprits in the majority of all ophthalmic infections. In bacterial conjunctivitis, the common offenders are *Staphylococci, Streptococcus pneumoniae, Pseudomonas aeruginosa, Klebsiella pneumoniae* and *Escherichia coli.*[3] Other sources classify bacterial conjunctivitis according to age, with *Staphylococcus aureus* the main culprit in adult infections and *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* common pathogens in children.[1,4] Gram-negative organisms (which could include Pseudomonas) are more likely culprits in contact lens wearers.[4]

More serious bacterial infections, which often lead to complications, include both *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. Chlamydial conjunctivitis is often resistant to standard bacterial conjunctivitis therapies and is treated with medications that target both the ocular and genital components of the infection.[1]

Conjunctivitis caused by *Neisseria gonorrhoeae* is defined as hyperacute bacterial conjunctivitis which tends to progress rapidly to corneal perforation. Timeous ophthalmological referral is thus essential.[1] This is also an infection that can be found in newborn babies as a result of vertical transfer during the delivery process – gonococcal ophthalmia neonatorum is a severe infection which can lead to further complications.[4]

Treatment

While the benefit of using antibiotics in a condition which can often spontaneously resolve has been questioned,[1] a Cochrane review found that when comparing the use of topical antibiotic to placebo in the treatment of bacterial conjunctivitis, clinical symptoms resolved and the infection cleared earlier. Additionally, the topical antibiotics were not likely to be associated with severe adverse effects.[2] Early on in the course of treatment (between days two and five), topical antibiotics, when compared to placebo, were found to improve clinical symptoms as well as lead to bacterial resolution. This improvement was also found between days six and ten, but this was a more modest improvement. However, also of note is that between days six and ten, 41% of case resolution was found in the placebo group.[2]

With regards to the treatment of ocular infections, empirical antibiotic treatment is generally employed and cultures are rarely used, unless in severe cases or in instances where initial treatment fails.[1,5]

In South Africa, first-line therapy in bacterial conjunctivitis is topical chloramphenicol, either used as eye drops or as ointment. Alternatives include fusidic acid, fluoroquinolones, aminoglycosides, all of which are topical formulations.[6]

Chloramphenicol displays a broad spectrum of activity, including numerous gram-positive, gram-negative and most anaerobic bacteria.[7] It is also first-line treatment in the UK, Australia and New Zealand,[8] but it is prescribed less in first world countries due to concerns regarding its adverse effect of aplastic anaemia.[9] However, claims of aplastic anaemia associated with topical use of chloramphenicol have been disputed.[2,7]

Fusidic acid, an alternative to chloramphenicol (especially in cases of demonstrated resistance to chloramphenicol),[6] has activity against mainly gram-positive organisms.[9] A study comparing the efficacy of fusidic acid to tobramycin found no significant difference in efficacy. However, ease of use was significantly different, where patients found the fusidic acid preparation easier to apply than that of the tobramycin.[10] Ease of use has been found to be an important indicator of compliance, with fewer instillations of the topical antibiotic improving compliance and theoretically enhancing efficacy and reducing resistance.[9] This would be apparent to any parent who has tried to administer topical eye medications to a non-cooperative toddler, and really, is there any other kind of toddler?

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In order to reduce new antibiotic threats, the Center for Disease Control and Prevention states that antibiotic resistance should be monitored.[5]

Ocular pathogens may not develop anti-infective resistance as readily. This may be due to the high concentrations in the ocular tissue due to the administration of topical dosing or direct injection.[5] Although the above is true for the older generation fluoroquinolones, it is not really evident in the newer, fourth-generation fluoroquinolones like moxifloxacin.

Minimal adverse effects are associated with topical use of the various fluoroquinolones, which include ocular discomfort, burning, itching, conjunctival hyperaemia, photosensitivity of the eye, lid crusting or oedema. Topical fluoroquinolones are not associated with tendinitis or arthropathy, which the systemic fluoroquinolones are known for.[11]

Topical aminoglycosides, such as tobramycin, have a broad spectrum of activity including various gram-positive and gram-negative bacteria, including *Staphylococcus spp., Haemophilus influenzae* and *Pseudomonas aeruginosa*.[9]

Chlamydial conjunctivitis in adults usually presents as unilateral conjunctivitis associated with a concomitant genital infection and is thus treated with systemic therapy, either oral azithromycin or doxycycline.[6] Moxifloxacin, a fourth-generation fluoroquinolone, is effective against chlamydia as a topical ocular fluoroquinolone. Neonatal conjunctivitis, transmitted by vertical transmission during labour from a mother infected by *Chlamydia trachomatis,* is treated with systemic erythromycin therapy.[6] Trachoma, a chlamydial conjunctivitis that occurs mostly in poorer socioeconomic countries, is treated orally with either erythromycin, azithromycin, or doxycycline.[6] Children who weigh less than 45 kilograms are treated with erythromycin, while children who weigh more than 45 kilograms but are less than eight years old, are given azithromycin and children older than eight years are treated with either azithromycin or doxycycline.[12] For macrolide allergy, during pregnancy or in infants less than six months old, topical tetracycline may be used.[12]

Azithromycin, one of the macrolide antibiotics, is a derivative of erthyromycin, but with an improved cover against gram-negative bacteria such as Enterobacteriaceae and *Haemophilus influenzae*. Azithromycin also displays similar activity against *Moraxella catarrhalis*.[13,14] Azithromycin provides good coverage for gram-positive organisms such as *Streptococcus pneumoniae*, as well as various atypical organisms, including *Chlamydia trachomatis,* legionella, mycobacteria and mycoplasma.[13,14] Gastrointestinal side effects are the most commonly observed adverse effects experienced by patients using azithromycin; however, azithromycin shows improved acceptability when compared to erythromycin.[14] The Food and Drug Administration (FDA) has cautioned azithromycin's use in patients with arrhythmias and/or a history of QT prolongation, as azithromycin can cause QT prolongation and torsades de pointes. This is important to consider when prescribing azithromycin with other drugs that can prolong the QT interval. Hearing loss has been associated with long-term use of azithromycin.[15] Topical preparations of azithromycin are also available and result in undetectable systemic concentrations. A study showed that topical azithromycin was a viable alternative for chlamydial trachoma in endemic areas. Furthermore, the topical preparation is well-tolerated with minimal adverse effects, which include ocular pain and burning on administration, as well as headaches.[16]

Doxycycline covers a large range of gram-positive, gram-negative and atypical organisms. Its gram-positive cover includes *Staphylococcus aureus, Streptococcus pneumoniae and Streptococcus pyogenes, Enterococcus faecalis, Listeria monocytogenes, Bacillus anthracis* and *Nocardia* species. Gram-negative coverage includes *Escherichia coli, Haemophilus influenzae* and *Moraxella catarrhalis* amongst others. Atypical coverage includes *Legionella pneumophila, Mycoplasma pneumoniae* and *Chlamydophila trachomatis*, as well as *Chlamydophila pneumoniae*. Doxycycline is also generally well tolerated, but does have several well-known side effects, including photosensitivity, tooth discolouration and bone deformities due to accumulation of the drug in both teeth and bones respectively, consequently limiting its use in children and pregnant women. Commonly occurring adverse events include gastrointestinal symptoms, but two of the more severe gastrointestinal symptoms are the possibility of oesophageal ulceration and *Clostridium difficile* diarrhoea. Other severe adverse effects include Stevens–Johnson syndrome and blood dyscrasias, but the incidence is rare. Doxycycline has also been associated with benign intracranial hypertension which may affect vision.[17]

Another type of conjunctivitis that requires systemic antibiotics due to the severity of the disease and possible complications, is conjunctivitis caused by *Neisseria gonorrhoeae.* Intramuscular ceftriaxone and oral azithromycin are given to both adults and neonates with this type of conjunctivitis. Additionally, neonates are given topical chloramphenicol ointment at birth to prevent this type of conjunctivitis.[6]

Ceftriaxone, a third-generation cephalosporin, has minimal adverse effects occurring in a small percentage of patients, including diarrhoea, nausea and vomiting, abdominal pain, candidiasis, headaches, dizziness, pruritus and skin rashes. Minimal serious adverse effects are experienced as ceftriaxone is administered as a single dose, but these may include haematological abnormalities, reversible biliary pseudolithiasis and rarely, pseudomembranous colitis. A more commonly experienced adverse effect is injection site reactions.[18] Its spectrum of activity covers *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Neisseria* species as well as methicillin-sensitive staphylococci, *Salmonella* and *Shigella* species. However, the Enterobacteriaceae are demonstrating resistance to all third-generation cephalosporins.[18]

Conclusion

While it is important to avoid unnecessary prescribing of antibiotics as one of the pillars of antibiotic stewardship, both topical

and systemic antibiotics do play a role in the treatment of bacterial conjunctivitis. Topical antibiotic preparations lead to clinical symptom improvement and bacterial resolution in less severe cases of bacterial conjunctivitis, whilst systemic antibiotic therapy used to treat the more severe chlamydial conjunctivitis and gonococcal conjunctivitis can prevent serious ophthalmological complications and also treats the sexually transmitted component of these infections.

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The GLP-1 receptor agonists: what's all the (cardiovascular) hype about?

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Abstract

Over four million people in South Africa are estimated to have diabetes. People diagnosed with diabetes have an increased risk of developing cardiovascular disease. Safety trials conducted on novel hypoglycaemic agents suggest that glucagon-like peptide-1 receptor agonists may afford cardiovascular benefits in this at-risk population. Selection of an agent from this class, as add-on treatment to metformin, should be individualised and based on accessibility, affordability, convenience of the dosing schedule, and tolerability.

Keywords: GLP-1 receptor agonists, cardiovascular disease, hypoglycaemic agents

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Introduction and epidemiology

Over four million people in South Africa are estimated to have diabetes.[1] People living with diabetes (PLWD) have an increased risk of microvascular and macrovascular disease, with an estimated prevalence of coronary artery disease among PLWD of 8.7% in South Africa.[1] The pathogenesis of increased risk of atherosclerotic cardiovascular disease in diabetes is multifactorial, and related to hyperglycaemia, hyper-insulinaemia, dyslipidaemia, inflammation, increased reactive oxygen species, endothelial dysfunction, hypercoagulability, and vascular calcification.[2] Mitigation of this increased risk requires lifestyle modification, glycaemic control and pharmacological management. Therefore, an understanding of the cardiovascular benefits and risks associated with the classes of anti-diabetic drugs utilised in type 2 diabetes mellitus is essential.[2]

Previously, a statistically significant reduction in HbA1c and short-term safety data was all that was required for approval of a glucose-lowering drug by regulatory authorities such as the US Food and Drug Administration (FDA). Safety signals of increased cardiovascular risk and cardiac failure with thiazolidinediones and sulphonylureas led to a change in policy for drug development.[3] Since 2008, the FDA has mandated that all new drugs developed for glycaemic control be assessed for safety with cardiovascular outcome trials (CVOT), evaluating the risk of major adverse cardiac events (MACE).[3] This composite endpoint includes myocardial infarction (MI), cerebrovascular accident (CVA), and cardiovascular mortality events, while some trials also include unstable angina and revascularisation events.[4] According to the FDA, an investigational hypoglycaemic agent is deemed to have an unacceptable level of risk if the upper bound of the 95% confidence interval (95% CI) for the hazard ratio (HR) of MACE exceeds 1.8 if the study is conducted preregistration, or 1.3 if conducted post-approval.[3,5]

Consequent to FDA requirements, we now have a body of evidence looking at the cardiovascular safety of newer hypoglycaemic agents, including the glucagon-like peptide-1 (GLP-1) receptor agonists.

Mechanism of action

Incretin hormones are released by the gut in response to an oral glucose load. Incretins, specifically GLP-1, reduce glucose levels through three important mechanisms: Firstly, GLP-1 stimulates insulin secretion, and this secretion is more pronounced during hyperglycaemia. During normo- or hypoglycaemia, GLP-1 stimulation of insulin secretion is reduced providing protection from further decreases in blood glucose.[6] Secondly, GLP-1 decreases the secretion of glucagon with a subsequent reduction in hepatic gluconeogenesis.[6] Thirdly, GLP-1 delays gastric emptying, reducing the postprandial increase in glucose and promoting satiety with resultant decrease in food intake.[6]

Endogenous GLP-1 has a short duration of action of 1–2 minutes and is rapidly degraded by dipeptidyl peptidase-4 (DPP-4) enzymes and cleared renally. To increase the duration of effect, GLP-1 analogues with longer half-lives were developed, that are not subject to degradation by DPP-4.

GLP-1 receptor agonists bind to the GLP-1 receptor and stimulate glucose-dependent insulin release to reduce blood glucose levels. As a class, GLP-1 agonists reduce HbA1c by 0.9–1.2% without clinically significant increased risk of hypoglycaemia, unless combined with insulin or sulphonylureas.[7] Furthermore, the effects of GLP-1 agonists on gastric emptying, satiety and resultant weight reduction are exploited in the medical management of obesity. Exenatide, liraglutide, dulaglutide, and semaglutide are GLP-1 receptor agonists registered for use in South Africa by the South African Health Product Registration Authority for the treatment of type 2 diabetes. Lixisenatide is a GLP-1 receptor agonist available in combination with insulin glargine.[8] These agents remain costly with single exit prices ranging from R350 to R2 400 depending on agent and dose, however, evidence from well-resourced settings

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Ozempic® is #1 in GLP-1 RA[5§]

2.8 million patients worldwide on Ozempic®[6‖]

*Results apply to Ozempic® across SUSTAIN trials, which included placebo, sitagliptin, dulaglutide, exenatide ER, insulin glargine, canagliflozin and liraglutide. SUSTAIN 4: Mean change in HbA_{1c} at Week 30 (+ MET ± SU), baseline 8.1% (N=1082): –1.2% Ozempic® 0.5 mg (n=362), (P<0.0001) and –1.6% Ozempic® 1 mg (n=360), (P<0.0001) vs –0.8% study-titrated insulin glargine (n=360). SUSTAIN 7: Mean change in HbA_{1c} at Week 40 (+ MET), baseline 8.2% (N=1201): –1.5% Ozempic® 0.5 mg (n=301) vs –1.1% dulaglutide 0.75 mg (n=299), (P<0.0001); –1.8% Ozempic® 1 mg (n=300) vs –1.4% dulaglutide 1.5 mg (n=299), (P<0.0001).

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Abbreviated Professional Information

Scheduling status: S4 **Name of the medicine:** OZEMPIC® **Qualitative and quantitative composition:** Semaglutide 1,34 mg/ml **Therapeutic indication:** Ozempic® is indicated: a) for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise, as monotherapy when metformin is considered inappropriate due to intolerance or contraindications, as combination therapy with oral anti-diabetic medicines (metformin, thiazoledinediones, sulphonylurea), basal insulin with or without metformin and pre-mix insulin. b) to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction or non-fatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease. **Posology and method of administration:** Ozempic® starting dose is 0,25 mg once weekly. After 4 weeks, the dose should be increased to 0,5 mg once weekly. After at least 4 weeks with a dose of 0,5 mg once weekly, the dose can be increased to 1 mg once weekly to further improve glycaemic control. Ozempic® is to be administered once weekly at any time of the day, with or without meals. Ozempic® is to be injected subcutaneously in the abdomen, in the thigh or in the upper arm. The injection site can be changed without dose adjustment. Ozempic® should not be administered intravenously or intramuscularly. The day of weekly administration can be changed if necessary as long as the time between two doses is at least 2 days (>48 hours). When Ozempic® is added to existing sodium-glucose cotransporter 2 (SGLT2) inhibitor therapy, the current dose of SGLT2 inhibitor can be continued unchanged. **Contraindications:** Hypersensitivity to semaglutide or to any of the excipients, a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2), pregnancy and lactation. **Special warnings and precautions for use:** Ozempic® should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. Ozempic® is not a substitute for insulin. Acute pancreatitis has been observed with the use of Ozempic®. Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, Ozempic® should be discontinued; if confirmed, Ozempic® should not be restarted. Patients treated with Ozempic® in combination with a sulfonylurea or insulin may have an increased risk of hypoglycaemia. The risk of hypoglycaemia can be lowered by reducing the dose of sulfonylurea or insulin when initiating treatment with Ozempic®. **Risk of Thyroid C-cell Tumours:** Cases of MTC in patients treated with liraglutide, another GLP-1 receptor agonist have been reported in the post marketing period; the data in these reports are insufficient to establish or exclude a causal relationship between MTC and GLP-1 receptor agonist use in humans. **Interaction with other medicines and other forms of interaction:** In vitro studies have shown very low potential for Ozempic® to inhibit or induce CYP enzymes and to inhibit drug transporters. The delay of gastric emptying with Ozempic® may influence the absorption of concomitantly administered oral medicines. The potential effect of Ozempic® on the absorption of co-administered oral medicines was studied in trials at Ozempic® 1 mg steady state exposure. **Fertility, pregnancy and lactation:** Ozempic® is contraindicated during pregnancy and lactation. **Undesirable effects:** The most frequently reported adverse reactions with Ozempic® in clinical trials were gastrointestinal disorders, including nausea, diarrhoea and vomiting. Adverse reactions by system organ class and absolute frequencies identified in all phase 3a trials listed here as Very common (≥1/10): Hypoglycaemia when used with insulin or sulfonylurea, nausea, diarrhoea; Common (≥1/100 to <1/10): Hypoglycaemia when used with other OADs, decreased appetite, dizziness, diabetic retinopathy complications, vomiting, abdominal pain, abdominal distension, constipation, dyspepsia, gastritis, gastrooesophageal reflux disease, eructation, flatulence, cholelithiasis, fatigue, increased lipase, increased amylase, weight decreased; Uncommon (≥1/1,000 to <1/100): hypersensitivity, dysgeusia, increased heart rate, injection site reactions, hypersensitivity, acute pancreatitis; Rare (≥1/10,000 to <1/1,000): anaphylactic reaction. **Overdose:** There is no specific antidote for overdose with Ozempic®. In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms. A prolonged period of observation and treatment for these symptoms may be necessary, taking into account the long halflife of Ozempic® of approximately 1 week. **Reg. No.:** 53/21.13/0497. For full prescribing information, refer to the Professional Information approved by the Regulatory Authority.

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suggests that these agents may still be cost-effective for patients that have failed monotherapy with metformin.[9,10] Local data would be required to assess the cost-effectiveness and affordability of these agents in South Africa.

Effects on atherosclerotic cardiovascular disease

In addition to their glucose-lowering effects, the GLP-1 agonists reduce the risk of cardiovascular disease via a reduction in atherosclerotic plaque formation and rupture, inflammation, and vasoconstriction.[11] Matrix metalloproteinase-2 (MMP2), an enzyme produced by vascular cells, promotes arterial remodelling in atherosclerosis. MMP2 concentrations are increased in patients with type 2 diabetes and cardiovascular risk factors. A previous animal study showed that MMP2 expression was reduced in diabetic rats after exenatide or GLP-1 administration using an adenovirus vector.[12] Improved endothelial function may also be related to an increase in nitric oxide production and reduced reactive oxidative species production in response to GLP-1 receptor agonists.[11] Other direct effects of the GLP-1 receptor agonists include the decreased expression of inflammatory cytokines and a reduction in systolic blood pressure, which appear independent of the degree of weight loss.[6] Atherosclerotic cardiovascular disease risk is further attenuated via a reduction in low-density lipoprotein (LDL) and triglycerides, a reduction in body weight, an increase in adiponectin (an adipokine protein known for its anti-inflammatory effects), and a reduction in albuminuria.[11]

Evidence for benefit in atherosclerotic cardiovascular disease

Several meta-analyses ("critically low" quality rating)[13] have reported a beneficial class effect of various GLP-1 agonists on MACE.[14-17] Of these, one meta-analysis examined all GLP-1 receptor agonist CVOTs published before June 2021 and included the results of 60 080 patients followed up from between 1.3 to 5.4 years. In this study, pooled analysis found that the risk of MACE was reduced by 14% (HR 0.86; 95% CI 0.79–0.94; $p = 0.006$) in GLP-1 agonist treatment groups, as compared to placebo. Treatment with GLP-1 agonists was associated with a 16% reduction in risk of MACE (HR 0.84; 95% CI 0.79–0.90; $p < 0.001$) in patients with established cardiovascular disease (secondary prevention population). In comparison, patients without established cardiovascular disease (primary prevention population) had a non-significant 6% reduction in risk of MACE (HR 0.94; 95% CI 0.83–1.06; $p = 0.33$).[17] Another meta-analysis ("critically low" quality rating)[13] which published a similar 14% reduction in risk of MACE (HR 0.86; 95% CI 0.80–0.93; $p < 0{\cdot}0001$), reported a number needed to treat of 65 (95% CI 45–130) patients over three years to prevent one event.[16]

Despite the lack of robust evidence for use in the primary prevention population, the latest guideline from the American Diabetes Association recommends the use of a GLP-1 receptor agonist to reduce the risk of MACE in people living with type 2 diabetes and established atherosclerotic cardiovascular disease, as well as those with multiple risk factors for cardiovascular disease.[18]

For individual components of MACE, GLP-1 receptor agonist treatment was associated with statistically significant reductions in risk of cardiovascular mortality and non-fatal stroke, but not non-fatal MI.[17] In stand-alone trials, exenatide (EXSCEL trial) and lixisenatide (ELIXA trial) failed to demonstrate a cardiovascular benefit, despite no difference to placebo in terms of safety.[19,20] Conversely, liraglutide (LEADER trial), semaglutide (SUSTAIN-6 trial), and dulaglutide (REWIND trial) all demonstrated benefit, but head-to-head trials examining superiority between agents in the class are lacking.[21-23] It is uncertain if this disparity in cardiovascular benefit across agents relates to differences in study design alone or to the inherent pharmacodynamic and pharmacokinetic properties of each agent.[11] For example, exenatide and lixisenatide are based structurally on exendin-4 (a hormone found in the saliva of the Gila monster that mimics GLP-1), whereas albiglutide, dulaglutide, liraglutide, and semaglutide are structurally similar to endogenous GLP-1.[16]

Safety and adverse effects

Common adverse effects associated with GLP-1 receptor agonists are gastrointestinal, including nausea, vomiting, and diarrhoea, which may contribute to reported discontinuation rates of between 4.5 and 13.2% across trials.[6,8] Gastrointestinal adverse events may be the result of direct effect on the central nervous system, in addition to delayed gastric emptying and increased smooth muscle activity and motility in the colon. The frequency appears to be dose-related and more prevalent when combined with metformin.[24] In a meta-analysis examining adverse effects, nausea, vomiting and study withdrawal rates were found to be lower with the longer-acting GLP-1 agonists, such as liraglutide and dulaglutide, as compared to the shorter-acting agents lixisenatide and exenatide. Semaglutide was not included in this meta-analysis as it was not yet registered for use in diabetes at the time the analysis was conducted.[24]

Based on preclinical studies, concerns of increased risk of pancreatitis, pancreatic cancer, cholecystitis, and medullary thyroid cancer associated with GLP-1 receptor agonists, have led to the exclusion of participants with a history of these conditions from subsequent clinical trials. The pathophysiological mechanism of these serious complications is related to the expression of GLP-1 receptors by thyroid C cells and the pancreatic duct.[6,11] Three meta-analyses ("critically low" quality)[13] did not show an increased incidence of pancreatitis, pancreatic cancer, or thyroid cancer associated with GLP-1 receptor agonist use.[14-16] Importantly, most trials for these agents were of limited duration, excluded patients at increased risk for these conditions, and were not powered to detect these rare events.

Overall, these results suggest that GLP-1 receptor agonists are safe to use, however, pharmacovigilance is ongoing.[25] For example, a registry to monitor the incidence of medullary thyroid carcinoma associated with GLP-1 agonist use has been mandated by the FDA

as a specific post-marketing requirement.[26] It remains prudent to avoid the use of GLP-1 receptor agonists in patients with a history of pancreatitis, pancreatic cancer, medullary thyroid cancer, or multiple endocrine neoplasia type 2 (MEN 2).[7,8]

Conclusion

Meta-analyses of pooled data for GLP-1 receptor agonists suggest a class protective effect in PLWD for atherosclerotic cardiovascular disease. In randomised controlled trials, liraglutide, semaglutide, and dulaglutide (all approved for use in South Africa) have demonstrated a reduction in MACE. Extending the use of these agents for the primary prevention of atherosclerotic cardiovascular disease in PLWD currently lacks robust evidence, and the cost-effectiveness of this indication is debatable. GLP-1 receptor agonists may be a useful adjunctive treatment option to metformin in patients with uncontrolled diabetes, established atherosclerotic cardiovascular disease, obesity, and problematic hypoglycaemia. However, the decision to initiate GLP 1 agonist therapy should be individualised and based on affordability.

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Conflict of interest

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Anaemia in chronic kidney disease

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Abstract

Anaemia, occurring in over 50% of patients with stages 3 to 5 chronic kidney disease (CKD), often causes fatigue, shortness of breath, cardiac dysfunction and cognitive impairment. The major causes include disorders of iron metabolism (both iron deficiency and iron blockade) and erythropoietin deficiency. Treatment should be aggressive, and treated to specific targets. Nutritional deficiencies should be treated first, and only once replete, should erythropoiesis-stimulating agents (EPO-stimulating agents [ESAs]) be considered. Careful consideration must be given to the adverse effects of ESAs, and prescribed only after discussion with the patient. Patients with refractory anaemia, rapidly deteriorating glomerular filtration rate (GFR), and who have stage 3–5 CKD should be referred timeously to a nephrologist.

Keywords: anaemia in chronic kidney disease (AiCKD), haemoglobin, iron, erythropoietin, uraemic toxins

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Introduction

Anaemia in chronic kidney disease (CKD) is present in over 50% of patients with a glomerular filtration rate (GFR) less than 60 ml/min/1.73 m^2 and increases exponentially as the GFR falls.[1] This is compared to an incidence of approximately 1% in patients with a GFR above 60.[2] Anaemia in CKD (AiCKD) is defined by the Kidney Disease: Improving Global Outcomes (KDIGO) group as a haemoglobin concentration less than 13.0 g/dl in adult males and 12.0 g/dl in adult females, and is identical to the definition by the World Health Organization.[3,4] Strict management of anaemia is vital, as both lower and higher haemoglobin concentrations are associated with increased morbidity and mortality: Ma et al. found an increased all-cause mortality with AiCKD, while Palmer et al. found an increased incidence of stroke, hypertension and death at higher haemoglobin levels.[5,6]

AiCKD is often underrecognised as a cause of clinically relevant CKD symptoms, including reduced physical performance, fatigue, shortness of breath, insomnia and cognitive impairment.[7,8] Similarly, anaemia can increase cardiac output, leading to left ventricular hypertrophy, angina and cardiac failure.[7,9] Therefore, understanding and reversing the causes of AiCKD is vital. The pathophysiological causes of AiCKD can be broadly divided into major causes (disorders of iron metabolism [including chronic inflammation and loss of erythropoietin [EPO] production]), and minor causes (hyperparathyroidism, uraemic toxins and drug effects).[7]

Major anaemia factors in chronic kidney disease

The majority of anaemia cases in CKD are due to two major factors: disorders of iron metabolism (both iron deficiency and hepcidin-mediated iron blockade) and a relative EPO deviancy. CKD patients often have increased iron losses, decreased iron absorption and decreased reticuloendothelial iron recycling.[10] Total iron loss in a healthy individual is approximately 0.5 to 2.5 mg daily, while a patient with CKD loses 2.7 to 8.2 mg iron daily, occurring mostly via chronic bleeding (usually gastrointestinal) from uraemic platelet dysfunction, repeated phlebotomies and dialysis-associated losses.[7,10] The maximum daily iron intestinal absorption is estimated at 2–3 mg per day, leading to a net iron loss and thus leading to AiCKD.[7] This also underlies the reason why oral iron supplementation often fails in CKD patients. To compound this, CKD patients have a functional iron deficiency, thought to be mediated by increased hepcidin concentrations.[10,11] Hepcidin, an acute phase reactant, is released by the liver in response to inflammation.[10,11] Additionally, hepcidin is excreted in the urine, and therefore hepcidin levels increase as CKD progresses.[11] Hepcidin, via inhibition of ferroportin, impairs both iron absorption in intestinal enterocytes and iron recycling in macrophages and hepatocytes. This decreased iron availability limits erythropoiesis even in the presence of adequate total body iron stores; the so-called reticuloendothelial iron blockade.[10] These factors can often be ameliorated, to a large degree, by the intravenous administration of iron.

EPO is an oxygen-sensitive glycoprotein secreted predominately by fibroblasts of the renal cortex and outer medulla.[12] Red cell production is exquisitely sensitive to EPO, and red cell production can rapidly be increased by elevated EPO levels.[7,12] As CKD progresses, overall renal mass declines, as does the total number of renal fibroblasts, ultimately leading to a reduction of EPO production, and hence a normochromic normocytic anaemia.[10,13] This can be corrected by administration of recombinant EPO analogues, once other causes of anaemia have been treated.

Minor anaemia factors in chronic kidney disease

Secondary hyperparathyroidism (SHPT) is a common complication of CKD, and often manifests at CKD stage 3 or later.[3,14] Raised parathyroid hormone (PTH) has been associated with anaemia, and hyporesponsiveness to EPO-stimulating agents

(ESAs).[14] Additionally, parathyroidectomy has been associated with improved haemoglobin levels, as well as restoration of responsiveness to ESAs.[15] Lastly, there is some evidence that increased PTH may lead to bone marrow fibrosis.[14,15] While the role of SPTH in AiCKD is established, its effect is modest; hence clinical priority in AiCKD should be targeted at replenishing EPO and iron stores, and thereafter the focus should turn to SHPT treatment.[14]

Uraemic toxins are known to decrease the survival of red blood cells.[3,7] The most important uraemic toxins associated with AiCKD are the polyamines such as spermine, spermidine, putrescine and cadaverine.[7] These polyamines are organic cations that are involved with cell growth and maturation, and in excess, reduce the proliferative activity of erythroid cells in the bone marrow.[7] The removal of such polyamines with dialysis is associated with improvement in anaemia symptoms, and highlights the need for regular adequate dialysis.[7,16]

Multiple drugs have been associated with anaemia, but in CKD, the most common causes are angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs).[7] Both these drug classes are extensively used in CKD due to their markedly beneficial renal and cardiovascular benefits.[17] However, a minor class side effect of both drugs, leading to anaemia, is sometimes seen.[18,19] This class effect is caused mainly by direct inhibition of the angiotensin II receptor on erythroid cells and by the accumulation of N-acetyl-seryl-aspartyl-lysyl-proline (usually degraded by angiotensin), a potent natural inhibitor of haematopoietic cell proliferation.[18,20] Additional drugs that can cause anaemia include the antimetabolites azathioprine and mycophenolate (via myelosuppression), and cyclosporin A and mTOR inhibitors (via haemolysis).[7] Therefore, it is always prudent to review drug usage in patients with AiCKD.

Treatment of anaemia in chronic kidney disease patients

Most guidelines, including the KDIGO guidelines, recommend that all patients diagnosed with CKD should be screened for anaemia at initial presentation and when clinically indicated. Additional ongoing AiCKD screening is indicated thereafter, and the recommended frequency increases with increasing CKD severity. A CKD stage-based AiCKD screening regimen, derived from the KDIGO guidelines, is shown in Table I.[3]

Table I: Frequency of testing for AiCKD

	Anaemia absent	Anaemia present
CKD stage 1–2	As clinically indicated	Hb three monthly
CKD stage 3	Hb yearly	Hb three monthly
CKD stage 4–5	Hb six monthly	Hb three monthly
CKD Stage 5 PD	Hb three monthly	Hb three monthly
CKD Stage 5 HD	Hb three monthly	Hb monthly

Tests required if anaemia is present: full blood count, differential count, absolute reticulocyte count, ferritin level, transferrin saturation, vitamin B_{12} and folate levels. CKD – chronic kidney disease, Hb – haemoglobin, PD – peritoneal dialysis, HD – haemodialysis

To investigate the AiCKD, KDIGO recommends the following minimum tests should be done: full blood count, differential count, absolute reticulocyte count, ferritin level, transferrin saturation, vitamin B_{12} and folate levels.[3] Treatment should be initiated based on the laboratory tests, and replacement should follow targets set out in Table II. Iron replacement should ideally be given intravenously in CKD stages 3–5, but a trial of oral iron can be administered for one to three months based on patient preference. Only once all deficiencies are replaced, should ESAs be considered.

Table II: Treatment targets for AiCKD

	Deficiency	Target
Hb	< 12.0 g/dl in females < 13.0 g/dl in males	10–11.5 g/dl (Up to 13.0 g/dl)*
TSAT	< 30%	> 30%
Ferritin	< 500 ng/ml	> 500 ng/ml
Vitamin B_{12}	Below local laboratory reference range	Within local laboratory reference range
Folate	Below local laboratory reference range	Within local laboratory reference range

* Higher Hb targets (up to 13 g/dl) can be targeted in certain patients, based on the patient's clinical symptoms and if the patient accepts the risks. Hb – haemoglobin, g/dl – grams per deciliter, TSAT – transferrin saturation, ng/ml – nanogram per millilitre

Once all deficiencies are corrected, and if AiCKD is still present, the use of ESAs should be considered. Initiation of ESAs should be considered carefully, and the risks of ESA usage (cardiovascular accidents, hypercoagulability and progression of non-benign lesions) versus the benefits (improvement of anaemia symptoms) should be discussed with the patient.[3] If the patient accepts the risk, this should be documented, and ESA use begun. The ideal haemoglobin target in KDIGO should ideally not be above 11.5 g/dl, but this can be individualised in patients willing to accept the risk, to a haemoglobin level of not more than 13.0 g/dl.[3]

Transfusion and use of whole blood products should be used only in emergencies, or after failure of nutritional support and ESA use. This is because the use of blood products is expensive, associated with many adverse reactions, and can potentially allo-immunise the patient against non-ABO blood antigens, increasing the risk of rejection events during future kidney transplant.[21] Therefore, the clinician should attempt to minimise transfusions, maximise nutritional and ESA usage, and be aggressive in investigating anaemias.

Conclusion

Anaemia in CKD is very common, is associated with adverse patient outcomes and can be difficult to treat. Treatment targets are lower than those in the general population (haemoglobin 10–11.5 g/dl), and can be easy to overshoot. Hence, the clinician should be careful in monitoring the AiCKD patient. The first step is to identify and treat nutritional deficiencies to target (iron, vitamin B_{12} and folate). Iron replacement in CKD stages 3–5

should ideally be intravenous. Once all nutritional deficiencies are treated, and if AiCKD is still present, ESAs can be initiated. The clinician should be aware that ESAs are associated with significant adverse effects and should only be initiated after discussing the risks with the patient. Blood transfusion for AiCKD remains an emergency stopgap, is associated with significant adverse events (short and long term) and should only be used in emergencies. If all of this fails, then referral to a nephrologist should occur for further in-depth anaemia assessment and treatments.

Key learning points

- Anaemia is present in over 50% of CKD stage 3–5 patients
- Iron deficiency is the most common cause of anaemia in CKD
- Iron should ideally be replaced intravenously in CKD stages 3–5
- All nutritional deficiencies (iron, vitamin B_{12} and folate) should be replaced before ESAs are initiated
- Blood transfusions should be reserved for emergencies only
- Nephrology consultation for AiCKD should occur in the following instances:
  - Refractory anaemia causes such as:
    - Secondary hyperparathyroidism
    - Severe uraemia
    - Suspected drug toxicities
  - For patients with CKD stages 3–5
  - For patients with a rapidly deteriorating GFR

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Bacterial vaginosis: an overview

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Abstract

Bacterial vaginosis (BV) is a commonly-occurring and well-studied cause of vaginal discharge. It is characterised by typical and unsettling symptoms, with an array of risk factors and complications associated with the condition. Treatment is aimed at reducing symptoms and preventing any further complications or infections. This paper is intended to provide a review of recent information on the pathophysiology, an overview of the clinical presentation, complications and treatment of bacterial vaginosis.

Keywords: bacterial vaginosis, biofilm, anaerobes, metronidazole, clindamycin

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Introduction

Bacterial vaginosis (BV) is a common condition caused by an overgrowth of bacteria in the vagina, known to affect a lot of women all around the world.[1] Discoveries on the cause and clinical presentation have expanded the knowledge of health practitioners regarding the disease, leading to therapy discovery and advancement, effective patient education, and ultimately improving the quality of life of the patient.[1] BV is the most common cause amongst all the known causes of vaginal discharge and is characterised by a malodorous vaginal discharge in women of childbearing age.[2] Those patients most severely affected experience an offensive, fishy-smelling discharge, which recurs frequently, often around the time of menstruation.[1,2] In others, BV may be transient and asymptomatic in nature.[1,2] The condition usually responds to treatment with antibiotics but can relapse rapidly; the reported rates of relapse are more than 50% within 3–6 months.[2] This points to the fact that there is a need for alternatives to antibiotics and to find a way to intercept relapses.[1,2] BV is very common, but its exact prevalence varies and depends on the patient population in question.[1,2] It may be diagnosed both clinically and microbiologically.[1,2] Some recent studies imply that it is sexually transmitted, with more pathogenic strains of *Gardnerella vaginalis (G. vaginalis)* being identified and recovered in the male partners of females diagnosed with BV.[1,2] It was also stated to be a risk factor in people having multiple sexual partners. In contrast, early studies reported findings of an estimated 12% of virgin female participants diagnosed with BV showing that the disease can be seen in females who have not had sexual intercourse.[1,2]

Pathophysiology

The presence of so-called vaginal clue cells, which are squamous epithelial cells coated with the anaerobic Gram-variable *G. vaginalis,* and other anaerobic bacteria, points to a diagnosis of BV.[3] The description and occurrence of clue cells have been consistent in the studies of BV, and also recognised in the Amsel criteria, which is widely regarded as a highly effective tool in diagnosing BV.[3] *Gardnerella* species have been implicated in samples of cells coated with Gram-variable bacilli.[3] With advances in microbiological techniques, it has been possible to demonstrate, in non-specific vaginitis, a change of vaginal microflora, which forms the basis of the pathophysiology of the disease.[4] Evidence has shown that a wide variety of pathogenic bacteria may be associated with this condition. These include *Mobiluncus*, *Bacteroides* species, Peptostreptococci and *Mycoplasma*, as well as *G. vaginalis*, *Ureaplasma urealyticum*, *Streptococcus viridans* and *Atopobium vaginae.*[5]

The characteristics of the vaginal microbiota are known to undergo changes over the course of a female's lifetime, and the nature of these changes may be influenced or modulated by a wide variety of factors. These include hereditary predisposition, as well as the levels of circulating oestrogen in her bloodstream.[6] Also refer to the common risk factors listed in Table I.

The role that vaginal *Lactobacilli* can play as a boundary of defence against various vaginal pathogens has also been elucidated.[5-7] It has been shown that vaginal *Lactobacilli* produce hydrogen peroxide (H_2O_2), a unique characteristic that allows these organisms to sustain a vigorous and healthy vaginal microbiota. Studies have shown this critical process to be abated in a patient with BV.[5-7]

Hydrogen peroxide-producing *Lactobacilli* have been shown to provide quite considerable support in the prevention of increased concentrations of the potentially pathogenic anaerobes that are habitually present in the vaginal flora.[5-7] With a loss of *Lactobacilli*, the vaginal pH becomes more alkaline and much higher concentrations of vaginal anaerobes start to appear.[7] Subsequently, the multiplying anaerobes start to produce an abundance of proteolytic carboxylase enzymes, which break down vaginal peptides into a range of unstable, volatile amines that are ill-smelling. This is accompanied by increased vaginal transudation and squamous epithelial cell exfoliation.[7] These signs form part of the typical clinical appearance of patients with BV[8]

Table I: Associated risk factors, clinical features and possible complications of bacterial vaginosis[13-17]

Associated risk factors	Clinical features	Possible complications
• Recent antibiotic use • Decreased oestrogen production • Wearing an intrauterine device (IUD) • Douching • Sexual activity that could lead to transmission (e.g. having a new sexual partner or a recent increase in the number of sexual partners)	• Vaginal odour, the most common symptom of BV, often recognised only after sexual intercourse. The alkalinity of semen may cause a release of volatile amines from the vaginal discharge and cause a fishy odour • Mildly to moderately increased vaginal discharge • Vulvar irritation (less common) • Dysuria or dyspareunia (rare)	• Preterm delivery in pregnant women • Low birth weight babies • Pelvic inflammatory disease (PID) • Post-abortion sepsis • Post-caesarean section endometritis • Herpes simplex virus type 2 (HSV-2) • Gonorrhoea • Chlamydia and *Trichomonas* infection • Increased rates of HIV acquisition

It has been suggested by many studies with significantly increasing evidence,[9] that *G. vaginalis* is the main pathogen that causes BV. In addition, it has recently been supported that the development of a biofilm may be a required component of this process of developing a gradual overgrowth of stable anaerobic vaginal flora.[9,10] A cohesive form of *G. vaginalis* adheres to the vaginal epithelium and then forms the framework to which other species attach.[11] *G. vaginalis* accounts for 90% of the bacteria in the biofilm of the microbiota on the epithelial surfaces of vaginal biopsy specimens, while *Atopobium vaginae* made up most of the remainder.[12,13]

The associated risk factors, clinical features and possible complications of BV are summarised in Table I.

Management and treatment of bacterial vaginosis

Antibiotics are the mainstay of therapy for symptomatic BV, but asymptomatic women with *G. vaginalis* colonisation do not need treatment.[14]

Goals of treatment

The main treatment goals in this setting are:[14]

- Relief of symptoms in women with symptomatic infection.
- Prevention of postoperative infection in those with asymptomatic infection prior to abortion or hysterectomy.

Non-pregnant women

In non-pregnant women with symptomatic BV, the following course of treatment is typically recommended:[18,19]

- A single dose of 2 gram of metronidazole can be used, but metronidazole 400 mg orally, twice daily for five days is more effective; **OR**
- Metronidazole gel 37.5 mg/5 gram (one full applicator) intravaginally, daily at night for five days; **OR**
- Clindamycin cream 20 mg/gram (one full applicator) intravaginally at bedtime, daily for seven days.

Alternatively, the following may also be considered:

- Clindamycin 300 mg orally, twice daily for seven days; **OR**
- Clindamycin ovule (vaginal suppository) 100 mg intravaginally, once daily for three days; **OR**
- Tinidazole 2 gram orally for two days; **OR**
- Tinidazole 1 gram orally, once daily for five days.

Pregnant women

The treatment options during pregnancy are as follows:[19,20]

- Metronidazole 400 mg orally, twice daily for seven days; **OR**
- Metronidazole 200 mg orally, three times daily for seven days; **OR**
- Clindamycin 300 mg orally, twice daily.

Metronidazole is considered safe even in the first trimester and does not appear to contribute to low birth weight, premature birth, or birth defects.[19]

Breastfeeding women

Women with symptomatic BV who are breastfeeding should be treated. Of note, clindamycin has the potential to cause adverse effects on the breastfed infant's gastrointestinal flora, so the infant should be monitored for diarrhoea, candidiasis (thrush, diaper rash) or, rarely, blood in the stool, indicating possible antibiotic-associated colitis. Clindamycin vaginal cream is preferred for use in breastfeeding women, because of the lower incidence of unwanted systemic effects.[21]

Sexual partners

There is no data to support the treatment of asymptomatic sexual partners.[22] It is not necessary to treat male sexual partners of affected women because there seems to be a lack of robust evidence that the woman's response to therapy, and the associated risk of relapse, may be influenced by the treatment of her male sexual partner.[22] However, some studies have reported reduced rates of recurrence when male sexual partners used condoms routinely during coitus or when women remained abstinent.[22]

Conclusion

BV is a commonly-occurring condition of the female sexual tract, mostly associated with the overgrowth of pathogenic, anaerobic bacteria in the presence of a suitable biofilm, an adverse change in the vaginal pH, or a lack of H_2O_2-producing *Lactobacilli* in the vagina. Symptomatic BV warrants proper antibiotic treatment, either locally or systemically, even in pregnant women and breastfeeding mothers. Effective treatment will reduce the

likelihood of complications and provide much-needed relief of the unpleasant symptoms associated with this condition.

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A competent review of computer imitations of pharmacokinetic and pharmacodynamic arrangements

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Abstract

Computer simulation in the field of pharmacokinetics and pharmacodynamics or in silico modelling is the need of the hour in the biomedical field. A computer simulation (CS) is a program run on a computer that uses step-by-step methods to explore the approximate behaviour of a mathematical model. The mathematical models enable the computational simulation of real-world systems. As the program is executed, the mathematical dynamics that arise constitute an analogue of the real-world system's behaviour. Computer simulations thus offer a means of quantitatively and qualitatively simulating, analysing, and visualising complex biological processes. Furthermore, in silico studies may help facilitate the research process by embedding ease and efficiency through computational simulations. This article explores the importance of computer programs for the simulation of in silico experiments with the help of mathematical descriptions or models. The current review summarises the various CS models for different drugs with their outcomes. The major challenge that seems to emerge is the need for quantitative, testable, and validated frameworks for the joint analysis of large data sets available in disparate formats and focused on different biological scales. The solution(s) to this problem will require a diverse set of disciplines, including not only biology and pharmacology but also (bio) engineering, computer science, (applied) mathematics and physics, and (bio) statistics. The study summarises and gives a brief review of recent biocomputation developments that are potentially relevant to drug development.

Keywords: discrete, mathematical model, pharmacodynamics, pharmacokinetic, stochastic process, computer simulation, in silico modelling

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Introduction

No knowledge of the anthropological past, including the overview of private figures and the World Wide Web's current global presence, may have completely changed the outcomes of a number of corrections. The multiparty desire of this powerful expertise concurs with us to quickly and effectively converse sound, observable, and trustworthy evidence.[1]

What is referred to as "biocomputation," or the creative modification of genetic and biomedical discoveries from a diligent endeavour, which is frequently reserved for bench and field researchers in a discipline based on the immediate availability of information and data mining, is one area that has greatly benefited.

However, clearly outlining what is exactly entailed by "biocomputation" or "biomedical simulations" is often a challenge.[2] Systems biology and bioinformatics are increasingly used in multiple settings, but the multiple meanings behind them, especially the expectations associated with these technologies, do not always give a clear picture.

Some experts even draw a distinction between "biomedical informatics" and "bioinformatics," not unlike those who distinguish between "bioengineering" and "biomedical engineering." The very fact that biomedical computation has become so pervasive has made it difficult to draw clear boundaries between fields of study and practice. It is difficult to clearly establish what areas of knowledge the practitioners using computer modelling in the biomedical sector have. Clinical trial simulation includes therapeutic drug monitoring, pharmacogenomics, molecular engineering, computer-aided drug design, and clinical record management.[3]

The focus on "discovery science" initiatives like the Human Genome Project and the various databasing initiatives required to somehow coordinate and manage the growing amount of bioinformation being generated by thousands of laboratories around the world have facilitated and, in a very real sense, motivated the information revolution in biology.

This has coincided with a scientific change of emphasis that is best tracked through the different interpretations and meanings associated with the phrase "systems biology" in the past few decades to date.[4-6] According to Guyton and other holistic physiologists, a living homeostatic system was considered comprised of a series of interacting parts, or subsystems, an understanding of which was deemed essential to comprehension of the complex dynamics of the whole.[7]

However, the starting point at that time was the intact system, as it was believed that only through information gathered on the macroscopic behaviour of the whole could one understand the inner workings of the parts. Direct investigation of the living

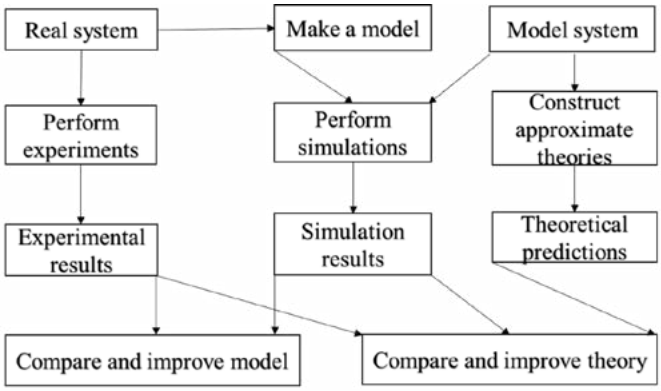

Figure 1: Process of building a computer model, and the interplay between experiment, simulation, and theory improvement

system was essential since Aristotle's proposal that "the whole remains more than the quantity of the parts."[8] The approach was "top to bottom".

This perspective changed with the development of molecular biology, which made it possible to examine the parts themselves with a previously unheard-of level of biophysical detail. According to researchers, a thorough study of the components would eventually result in a comprehension of how they interact and work together to affect the dynamic functioning of the whole living system. This led to a change in the paradigm of clinical sciences toward basic sciences, and of pharmaceutical sciences toward molecular pharmacology. This strategy is known as "bottom to top".

Computer simulation (CS) or a computer model, is a processor programme writer that attempts to simulate an abstract model of a particular system.[9] With computational resources available today, large-scale models of the body are available for sale to produce realistic simulations.

It includes the practice of CS of genetic classifications with cellular subsystems (such as by way of the systems of metabolites and enzymes that comprise metabolism, signal transduction, pathways, and gene regulatory networks) to investigate and envision the composite influences of these cellular methods (Figure 1).

Computer simulations

This has been successfully applied in various industries (e.g., automobiles, aerospace) to make product development more efficient.[10,11] The use of CS in support of clinical drug development to predict the clinical outcomes of planned trials has been recommended.[12] The methodological basis for this approach is provided by pharmacokinetic (PK) and pharmacodynamics (PD) mathematical models together with Monte Carlo techniques. Fashionable the current broadside, the straightforward concepts of medical experimental imitation remain announced and proved through the sample of oral antineoplastic medicine. It has been demonstrated that CS aids in evaluating the significance of project geographies, arranged security, and medication effectiveness valuation, which were previously difficult to find. An indication of current imitation possessions through admiration of exercise and computer software is provided.[13]

Table I: A few different types of simulation models and their main features and capabilities

Name of the CS	Features	Aptitudes
AIMSUN	Microscopic	Freeways, surface roadways, signal-activated intersections, dynamic traffic management, variable message signs, telematics, and 3D animation
CORFLO	Macroscopic	Surface streets and freeways
Corridor Simulation	Microscopic	Freeways, actuated signals, weaving lanes, accidents, variable message signs, surface streets, and 2D animation
DynaMIC	Mesoscopic and real time	ATIS and ATMS operation, dynamic network state estimation, various real-time scenarios, and trip simulation
Hystra	Hybrid	Combining macro- and micro-scale models, both of which are based on the LWR traffic flow theory
Integration	Mesoscopic	Surface roadways, freeways, traffic scheduling, I.T.S., toll booths, car emissions, and HOV
Kronos	Macroscopic	Lane switching, merging, diverging, and weaving on freeways, as well as the formation of lines of traffic and the spread of congestion on the motorway and its ramps
MicMac	Hybrid	The microscopic model SITRA B+ and the macro model SIMRES are connected, and the models are synchronised sequentially
MITSIMLab	Microscopic	ATIS and ATMS
PARAMICS	Microscopic and distributed	Roundabouts, surface streets, freeways, transport operations, crowded networks, and 3D animation
SATURN	Microscopic	Separate intersections and traffic flow
Traffic	Microscopic	Pedestrians, roundabouts, actuated signals, surface streets, and 3D animation
VISSIM	Microscopic	Pedestrians, ramp metering, freeways, surface streets, transit operations, and 3D animation
Waves	Macroscopic, discrete, and deterministic	Throughput, bottlenecks, lines, ramp metering, and incident management are all related to freeways

ATIS – Advanced Traveler Information System, ATMS – Advanced Traffic Management System, LWR – Lighthill-Whitham-Richards, I.T.S – Intelligent Transportation System, , HOV – High Occupancy Vehicle

Types of computer simulation

Processor representations remain unpublished, rendering in the direction of numerous sovereign braces of quality, and counting (Table I).[14-16]

An alternative method of classifying representations is to look at the primary information constructions. For time-stepped simulations, there are two foremost programs:[17]

- Simulations that store their information in even lattices and necessitate individual next-neighbour admittance are termed stencil codes. Several CFD submissions go to this group.
- If the fundamental chart is not a steady lattice, the prototypical whitethorn belongs to the mesh-free technique.

Equivalences describe the associations among essentials of the demonstrated scheme and the effort to discover a state in which the arrangement is in balance. Such representations are frequently recycled in faking corporeal schemes as a meeker demonstrating a situation where previously active imitation is struggling.[18]

The self-driven imitations of prototype changes made by a scheme happen as a result of contribution cues, which are always shifting. To imitate unplanned or accidental events, stochastic representations use mistaken figure makers. A different occasion imitation supervises everything at all times. This includes impersonations of the maximum processor, logic tests, and fault trees. In this category of imitation, the simulant sustains a column of proceedings organised by the imitation period in which they would happen. The simulant declaims the file and inducts the original proceedings as the incident is handled. In the current era, it is unnecessary to perform the imitation. It is frequently more significant to admit the information fashioned by the imitation than to determine whether there are lucid imperfections in the project or the arrangement of proceedings.[19]

Differential-algebraic equations or differential equations can be numerically solved through constant self-motivated imitation (either partial or ordinary). The simulation programme periodically explains all the computations and statistical applications used to change the imitation's production and status. Aeronautical simulations, building and organisation simulations, biological procedure demonstrations, and electrical circuit simulations are a few examples of uses. These simulations were initially carried out on analogue computers, where the differential equations could be directly represented by different electrical components like op-amps. However, during the late 1980s, the majority of "analogy" imitations were still being monitored on conservative digital processors that behaved similarly to a comparable processor.[20]

A superior kind of separate imitation that does not depend on a perfect comparison through an original comparison container remains characterised officially as an agent-based imitation. In agent-based imitation, the separate things (such as fragments, compartments, foliage, or patrons) in the archetypal are indicated unswervingly (moderately more than by their compactness or attentiveness) and possess an internal state and a set of behaviour or rules that determine how the agent's state is updated from one time-step to the next.[21]

Dispersed replicas are routed on interconnected computers, possibly through the Internet. Simulations dispersed transversely by various congregation processers like this are frequently mentioned as "dispersed imitations".[21] There are some morals for dispersed imitation, with the Aggregate Level Simulation Protocol (ALSP), Distributed Interactive Simulation (DIS), the High-Level Architecture (simulation) (HLA), and the Test and Training Enabling Architecture (TENA).[22]

Uses

Analysis of things or systems that function in ways that cannot be simply or safely practical during their actual lifecycle is becoming more and more popular in CS. Imitations are especially useful for helping observers to measure and imagine how changing certain mechanisms within a scheme could make the operational elements of the system improve. Military simulations are really useful. Numerous applications of CS may be found in numerous scientific disciplines, including meteorology and the physical sciences,[23] etc.

Organ stimulation

The heart and liver were, in fact, the most thoroughly examined organs, while the kidney and brain similarly remained the focus of scientific demonstration. Several of the processer imitations for the heart and liver remained approved and available via distributed blood tissue exchange (BTEX) representations. Even though the amplified equal of feature and chronological resolve surely makes the decent fraternisation and consistency premises at the foundation of lumped parameter models less acceptable. It can be altered that the addition of organ-specific exhibiting through the overhead entire creature replicas would result in perfection in the PBPK method's finished "improved" (i.e., more physiologically sensible and reasonable) replicas of different organs. Whole-body systems are usually represented in one of two ways (lumped-parameter PK-PD model or physiological model) [24].

Lumped-parameter PK-PD model

The lumped-parameter PK-PD model is sometimes referred to as the "contributor model," the "lumped limitation model," and population PK and PD modelling. It condenses the description of how spatially distinct bodily systems behave into an analysis scenario including discrete objects that gauge how the spread scheme would behave under specific assumptions. By using modelling analysis and dosage regimen prediction, this study seeks to depict the PK and PD of a population and determine appropriate dose levels. The best definition of haemoglobin during this time was provided by a two-compartment linear model and body mass in relation to delivery capacity. The system's behaviour over time is predicted by a very modest number of discrepancy comparisons—between one and 10. The estimation of the population limiting values and their arithmetical circulation

is frequently, but not always, based on nonlinear degradation and nonlinear mixed-effects models. The same strategy can be applied in a cutting-edge, contradictory manner by employing replicas to produce synthetic information and, in the end, completing a comprehensive clinical trial simulation from scratch. Finished PK and PD are allowed according to the exposure-response thoroughfare chart. This categorisation of events is substantially similar to that which alerts CS of scientific investigations through the accumulation of perplexing but crucial factors like procedure adherence and dropouts.[25]

Rediscovering systems physiology in the 21st century

The organs in the organism under study are arranged physically similar to them. Although the illustration of the intact organism provided by the PK-PD and physiologically based PK (PBPK) models is basic, it does pose non-traditional challenges. For PK-PD, the purpose consists of finding the simplest model that can explain the observations. Officially speaking, the perception of "best" is problematic to define definitively. Often, the model range is driven by a stinginess standard that equilibrates model complexity with the actual data content provided by the capacities. An agreement workshop industrialised some time ago a set of "good practices" that can serve as supervision for model development, selection, and application.[26] As a result of changes following a different strategy, PBPK replicas are created. Because they surround previous knowledge about organ kinetics, their provisions, and their specific parameter values, the process of couture the model to the specific capacities is not as crucial.

If PBPK replicas' parameterisation is inaccurate, vague, or poorly matched to the medication, it might cause severe suffering in their predictive control. Numerous researchers have given PBPK right constructions and limitations obsessed with "medicine exact" and "non-medication exact," indicating that the perfect can undoubtedly be imprisoned about fundamental undercurrents that are common to all drugs and that further specification can be limited to the unique characteristics of a particular molecule.[27]

When dealing with model-based predictions, it is critical to specify limit and erection indecision. More details on how these limits can be specified are similarly provided underneath. The method occupied by PBPK modelling is not unrelated to the recently begun Physiome Project, a "shares tilt" of the hominoid organism whose development follows the broad strokes of the Human Genome Project.[28]

The absence of data on single-organ restrictions, such as permission fees and screen coefficients, frequently represents the rate-limiting stage for growing PBPK copies. A biomedical researcher would surely benefit from a complete perspective on them, such as the one offered by the Physiome Scheme. As we stated above, the Environmental Protection Agency (EPA) is also interested in the computer-based prediction of individual PK and has published a document outlining the technique for public discussion.[29]

The consideration of the molecular underpinnings of whole organism homeostasis continues to advance, but they have not yet been aggressively implemented in medication development, which is an important last point to make (where they would be most useful, one would expect, for between- and within-species scaling). It's noteworthy to notice that the main difficulties involved in fully modelling a whole organism (such as computing time, the complexity of exchanges, and model selection) are quite comparable to those involved in analysing proteomic or genomic data.

Presently, complications shift from the prosperity of the data set to the model preparation, whereas in the proteomic-genomic case, the primary source of difficulties is the sheer size of the data set. However, at least at present, explanatory tools are relatively straightforward.

Physiological modelling

This prototype is brought into practice by PBPK models (Figure 2). These replicas are on regular differential equivalences. However, they attempt to describe the organism and predominantly the interrelating organs in more detail, often by swelling the number of inconsistency assessments (from 10 to perhaps 30) and building appropriate connections between the organs that resemble their physical arrangement in the organism being studied.[30]

A compromise workshop industrialised some time ago a set of "good practices" that can serve as direction for model expansion, selection, and application. The stinginess criteria on that equilibria model difficulty with the actual evidence content provided by the measurements drive model selection. After a different approach, PBPK replicas emerge from the problem. PBPK replicas have significant extrapolative control uncertainty; their parameterisation is imprecise, poorly quantified, or not well personalised to the drug. It is stimulating to note that the leading encounters are for the detailed melding of the integral organism (computing time, the complexity of interactions, and model selection).

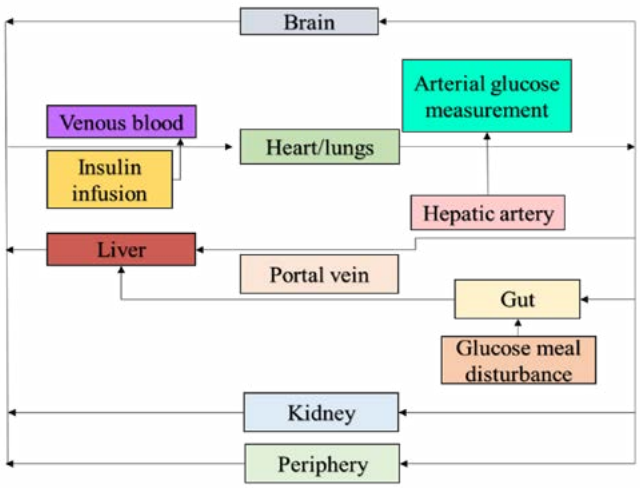

Figure 2: Physiological model of what?

Isolated tissue and organs simulation

The liver and heart remained the organs that had been researched the most, but the kidney and brain had also been the focus of precise, illuminating research. Since the heightened equal of aspect, numerous processor imitations targeting the heart and liver have been approved and made available through dispersed blood tissue exchange (BTEX) models and consistency theories by the foundation of taken limit imitations (Figure 3).

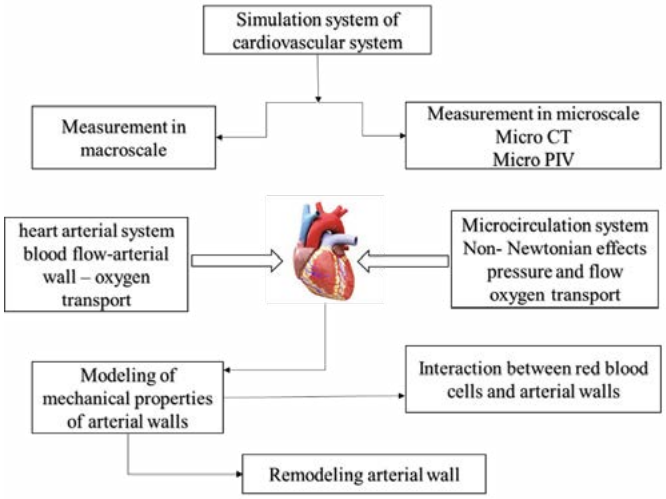

Figure 3: LabChart for cardiovascular circulation

It can be suggested that adding organ-specific manifestations demonstrating through the upstairs entire creature replicas would result in expansions aimed at the PBPK method's finished "improved" (i.e., more physiologically sensible and reasonable) replicas of specific organs. The main challenge is the compulsory shift from lumped to disseminated limit models.[31]

At the National Institute for General Medical Sciences at the NIH, the Centre for Demonstrating Integrated Metabolic Systems (MIMS) has as its assignment the growth and addition of in vivo organ-specific exact replicas.[32] These organ-specific exact replicas can positively forecast behaviours aimed at a variety of limits, including breaks, workouts, and several pathophysiological situations. The Microcirculation Physiome and the Cardiome are additional multi-centre projects focused on aspects of the physiome undertaking. The physiome of an entity's before-class physiological state is a report of the situation's practical behaviour. The physiome labels the physiological dynamic forces of the usual complete creature and remains erected upon data and assembly (genome, proteome, and morphome).[33] There is an enormous variety of software for PK and PD simulations.

Isolated organ research allows an organ to be studied in a controlled environment, free from external influences. Conditions such as temperature, the degree of oxygenation, available nutrients, and pH can be controlled for research purposes. Perfusion of an organ—typically the heart, lungs, liver, or kidney-whitethorn remains obligatory. Once the organ is positively upheld external to the figure, the situation of physiological occupation can be deliberated through an entire set of recordable limits such as force, muscle reductions, pressure, and biopotentials.[34]

Simulation instruments offer a wide range of high-quality products, systems, and solutions to meet your isolated organ research needs, including various tissue-organ bath systems. Lab Chart provides efficient software to measure and analyse changes in blood pressure, flow, and volume, as well as many additional functions for pharmacological and cardiovascular research. The authors also offer a Dose-Response Add-On, with analysis and a graphical display of dose-response data recorded in LabChart (Figure 3).

Computer simulations of the cell

Cellular-level CS is limited by the fact that there is a lack of universal agreement as it relates to the inner workings of several of the intracellular and membrane processes. Although using competing computer models would be an efficient way to select the best hypothesis among a slew of competing ones, this approach is rarely taken in cell biology, where experimental verification dominates the literature. Similarly, while understanding the cell, its receptors and channels, and the modalities of membrane transport may be a worthwhile scientific endeavour, it must be balanced in drug development against the constructive role of this information in accelerating the development process. Because several of these replicas await independent scientific validation, their use in drug development is perhaps not as widespread. These modelling paradigms are more aggressively used in the biomedical research arena. The Virtual Cell is an online repository of some of these models, making a CS of the whole cell available to its users' network.[35]

Another online repository of biophysical models is the CellML (an XML-founded rise linguistic aimed at telling exact models) website. The idea of "network" is very widespread in the models that focus on the cellular environment. Interactions between cells and within the intracellular milieu can clearly be observed as complex networks of signals, and thus the computer implementation of oriented networks is a simple approach to modelling this type of system. Some very interesting work has remained completely trendy in bacterial systems through a creative approach based on the exhaustive enumeration of the biochemical reactions taking residence within the cell. The system is then studied at steady-state because the dynamic parameters determining the time-varying biochemistry are largely unknown and the stoichiometry of the reactions is reasonably well identified.

Nevertheless, rather than being limiting, the study of the universe of possibilities (structurally restricted) related to all steady states in such a system has greatly increased our understanding of the long-term behaviour of simple animals exposed to a variety of external environments. It has created new avenues for investigation into the optimum bioreactor design as well as, more generally, how biological systems may choose to reallocate energy to various

components of the overall response network in order to adapt to changing environmental conditions.

Investigating signals within the cell provides a new level of complexity. This has been described for simple organisms by models integrating data at many levels, from genes to biochemistry to physiology. Signalling networks are increasingly complex concerning the networks discussed, dealing with material fluxes because the precise signalling modalities are largely unknown, which is a significant source of difficulties. New tools are being developed for this purpose.[36]

Conclusion

The study attempted to provide a brief review of recent biocomputation developments that are potentially relevant to drug development. The major challenge that seems to emerge is the need for quantitative, testable, and validated frameworks for the joint analysis of large data sets available in disparate formats and focused on different biological scales. The solution(s) to this problem will require a diverse set of disciplines, including not only biology and pharmacology but also (bio) engineering, computer science, (applied) mathematics and physics, and (bio) statistics. It seems that biology is currently at a crossroads where the "best" approaches to analysing and synthesising this rapidly growing corpus of information have not been developed yet. For drug development, the challenge is to formalise testable models of intact systems that would allow, for example, simulation and testing of all development steps of various therapeutic targets against the ever-changing landscape of human physiology. This will, in turn, require rapidly evolving professional expertise that can quickly and efficiently adapt to the shifting objectives of modern biomedical investigation.

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Solifenacin

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Introduction

Overactive bladder syndrome (OAB) is a chronic medical condition that can have a major effect on quality of life. OAB causes a frequent and sudden urge to urinate that may be difficult to control and can also lead to urinary incontinence.[1] First-line treatment starts with behavioural therapies such as bladder training, pelvic floor muscle exercises, and fluid management. After lifestyle interventions, anticholinergic drugs are the next step in treating OAB. Antimuscarinics are the drug class of choice for OAB symptoms and have proven efficacy.[1-3]

Indication

Solifenacin is indicated for the symptomatic treatment of OAB: symptoms of urinary urgency, frequent micturition and/or urinary incontinence.[4]

Mechanism of action

Solifenacin is in the group called urinary antispasmodics and is classified as a cholinolytic or otherwise known as an anticholinergic drug.[4]

Solifenacin is a competitive, specific cholinergic receptor antagonist. In vitro studies demonstrated that solifenacin binds to muscarinic receptors, with high affinity.[4]

Solifenacin works to decrease bladder activity by inhibiting contraction of the smooth muscle wall surrounding the bladder. Micturition normally occurs following stimulation of acetylcholine muscarinic M3 receptors within the detrusor muscle wall.[5]

Efficacy of solifenacin in OAB

In studies where the efficacy and safety of solifenacin was studied in patients with OAB, it was found that solifenacin was significantly more effective than placebo in reducing the mean number of episodes of severe urgency. Episodes of nocturia and incontinence were also significantly reduced when compared to placebo. The most common adverse effects with solifenacin were dry mouth and constipation and these adverse effects were mild to moderate.[6]

In a systematic literature review where the efficacy and tolerability of solifenacin 5 mg/day was compared to other oral antimuscarinic agents for the treatment of OAB, it was found that solifenacin is at least similar to other common antimuscarinics across the spectrum of OAB symptoms analysed and is more effective than tolterodine 4 mg/day in reducing incontinence and urinary urgency incontinence episodes. It was also found that solifenacin 5 mg/day has a lower risk of dry mouth compared with several other antimuscarinic agents.[7]

In an older review it was found that treatment with solifenacin was well tolerated by patients with few discontinuations due to adverse effects. It was also found that there was a high resolution and improvement rate due to the impact that solifenacin has on urgency that could be acknowledged as a key symptom of this syndrome.[8]

Solifenacin's efficacy has clearly been demonstrated in published studies for all symptoms of the OAB complex, with a high degree of tolerability and patient benefit.

Dosing and administration

For adults

The recommended dose is 5 mg once daily, if needed, the dose may be increased to 10 mg once daily.[4,9]

Special populations

Patients with renal impairment

No dose adjustment is necessary for patients with mild to moderate renal impairment (creatinine clearance > 30 ml/min). Patients with severe renal impairment (creatinine clearance > 30 ml/min) should be treated with caution and receive not more than 5 mg once daily.[4,9]

Patients with hepatic impairment

No dose adjustment is necessary for patients with mild hepatic impairment. Patients with moderate hepatic impairment should be treated with caution and receive not more than 5 mg once daily.[4,9]

The use of solifenacin is not recommended in patients with severe hepatic impairment.[9]

Potent inhibitors of cytochrome P450 3A4

The maximum dose of solifenacin should be limited to 5 mg when used simultaneously with ketoconazole or therapeutic doses of potent CYP3A4-inhibitors, e.g. ritonavir, nelfinavir, itraconazole.[4,9]

Method of administration

Solifenacin should be taken orally and should be swallowed whole with liquids. It can be taken with or without food, as is convenient.[4]

Warnings and special precautions

Other causes of frequent urination (heart failure or renal disease) should be addressed before treatment with solifenacin is undertaken. If urinary infection is present, an appropriate antibacterial therapy should be started.[4]

Solifenacin should be used with caution in patients with:

- clinically significant bladder outflow obstruction in the absence of clean intermittent catheterisation due to the risk of urinary retention
- severe renal impairment (creatinine clearance < 30 ml/min)
- moderate hepatic impairment (Child Pugh score 7–9). Not recommended in patients with severe hepatic impairment (Child Pugh score 10–15)[4,10]
- decreased gastrointestinal (GI) motility (severe constipation, ulcerative colitis) or GI obstructive disorders (pyloric stenosis) as it may increase the risk of gastric retention[10]
- hiatus hernia or gastro-oesophageal reflux and/or patients who are concurrently taking medicines (such as bisphosphonates) that can cause oesophagitis[4]
- known history of QT prolongation[4] or other risk factors for QT prolongation (e.g. concomitant use of medications known to prolong QT interval, electrolyte abnormalities).[9,10] QT-prolongation and Torsades de Pointes have been observed in patients with risk factors.[1] The risk for QT prolongation is dose-related.[9,10]
- controlled (treated) narrow-angle glaucoma. The use of solifenacin is contraindicated in uncontrolled narrow-angle glaucoma.[4,9,10]
- concomitant use of a potent CYP3A4 inhibitor, e.g. ketoconazole[4,9]
- autonomic neuropathy[4]
- safety has not been established in pregnancy and lactation[4]

According to the Beers Criteria, use should be avoided in elderly patients with delirium or at high risk of delirium as solifenacin may induce or worsen delirium.[9]

Due to the pharmacological effect of solifenacin, the drug may cause anticholinergic side effects that range from mild to moderate in severity.[4] The frequency and severity of anticholinergic side effects are dose-related.[4] Solifenacin may cause drowsiness and/or blurred vision, which may impair physical or mental abilities and patients must be cautioned about performing tasks that require mental alertness (e.g. operating machinery, driving).[4,10]

Other central nervous system (CNS) effects (e.g. headache, confusion, hallucinations, somnolence), have been reported particularly at treatment initiation or dose increase. Reduce the dose or discontinue if these symptoms persist.[10]

Interactions

Pharmacological interactions

Concomitant administration with other medicines with anticholinergic properties may result in more pronounced therapeutic effects and side effects. An interval of approximately one week should be allowed after stopping treatment with solifenacin before commencing other anticholinergic therapy.[4]

The therapeutic effect of solifenacin may be reduced by concomitant administration of cholinergic receptor agonists.[4,10]

Solifenacin can reduce the effect of medicines that stimulate the mobility of the GI tract, such as metoclopramide and cisapride.[4,10]

Pharmacokinetic interactions

Since solifenacin is metabolised by CYP3A4, pharmacokinetic interactions are possible with other CYP3A4 substrates, inhibitors, and inducers.[4]

Solifenacin showed no effect on the pharmacokinetics of oral contraceptives, warfarin, or digoxin.[4]

In summary

For the treatment of OAB, antimuscarinics have been used successfully for many years. The ideal antimuscarinic agent should effectively relieve the symptoms of OAB, with minimum of side effects, it should be available as a once-daily sustained release formulation and in dosage strengths that allow easy dose titration for most sufferers.[3,11] Solifenacin succinate was launched in 2005 and has been shown in both short- and long-term clinical trials to fulfil these requirements.[11]

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Full list of references available on request

solifenacin succinate 5 mg /10 mg

SOLESTAN

Bladder Control & Confidence

NEW

SOLESTAN

Solifenacin succinate 5 mg and 10 mg film-coated tablets[1]

INDICATIONS

For the symptomatic treatment of overactive bladder (OAB) syndrome:[1]

- Urinary urgency
- Frequent micturition
- Urge incontinence

EFFICACY OF SOLESTAN

Both 5 mg and 10 mg significantly improve:[2]

- Urgency
- Frequency, and volume voided
- Superior in terms of efficacy to tolterodine

Effective in:[2]

- Patients with severe OAB symptoms
- The elderly, and the mildly cognitively impaired

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S3 **SOLESTAN 5**: Each film-coated tablet contains 5 mg solifenacin succinate. Reg. No: 51/5.4/0258. S3 **SOLESTAN 10**: Each film-coated tablet contains 10 mg solifenacin succinate. Reg. No: 51/5.4/0259. For full prescribing information, refer to the Professional Information, approved by the medicines regulatory authority (SAHPRA).

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Presidential report 2023

Nhlanhla G Mafarafara
President, SAAHIP

Introduction

Nhlanhla G Mafarafara

The year 2022 can be summarised as being a year of transition back to the norm, but it's a new norm. A norm after a pandemic where we learn to trust in face-to-face meetings once more. Where we try not to panic when we hear a cough or sneeze nearby. Pharmacy through these past three years has shown great resilience. We have adapted and remained functional. We have led the fight against SARS-CoV-2. We have experienced loss, but we have survived. We are a thriving profession. Many have sometimes sacrificed their mental wellbeing for the sake of the health and wellbeing of the nation. Pharmacists on the ground remain committed to serving patients, however, structural challenges such as medicines stock-outs, dilapidated infrastructure, inequitable distribution of human resources, underfunding and many more, remain a threat to service delivery in their respective institutions. We thank all pharmacists and pharmacy support personnel for staying the course.

I am pleased to present the annual report, sharing the activities of the SA Association of Hospital and Institutional Pharmacists from 2022 to 2023.

National Executive Committee

During the AGM held in March 2022, the following people were elected into office:

a. President – Kaajal Chetty

b. Vice-President – Nhlanhla Mafarafara

c. National Secretary – Obey Madzingo

d. Honorary Treasurer – Hannes Stegmann

Unfortunately, our elected president, Kaajal Chetty had to step down from office effective 1 November 2022 as an opportunity to take up office within the PSSA presented itself. Thus, I assumed the office of president in accordance with the SAAHIP constitution. This was followed by further changes to the NEC. During the NEC meeting held on 19 November 2022, Obey Madzingo was elected by the NEC to fill up the Vice President's position, which left the National Secretary's office vacant. Armand Algra was then elected as National Secretary in the same meeting. The current NEC is presented in Table I.

Table I: SAAHIP National Executive Committee

Nhlanhla G Mafarafara – National President	Kesentseng Mahlaba (Northern Gauteng)
Obey Madzingo – Vice President	Sylvester Rasekgotoma (Limpopo)
Armand Algra – National Secretary	Marelee du Plooy (North-West)
Hannes Stegmann – Honorary Treasurer	Seshnee Moodley (Eastern Cape)
Shawn Zeelie – Past President	Danielle Tshabalala (Northern Cape/ Free State)
Rashmi Gosai (Southern Gauteng)	Alex Wehmeyer (co-opted)
Paul Voigt (Western Cape)	Lourens van der Merwe (co-opted)
Vusi Dlamini (KwaZulu-Natal Inland)	Lorraine Osman (co-opted)
Nomfundo Zwane (Mpumalanga)	Refiloe Mogale (co-opted)
Thandeka Njapha (KwaZulu-Natal Coastal)	Joggie Hattingh (co-opted)

I am truly honoured to have worked with Kaajal as her deputy and thus express gratitude to her for paving the way for presidential success. We extend our gratitude to the past branch chairpersons, Armand Algra (NW), Rhulani Maluleke (LP), Carrie de Beer (WC), Nondumiso Makwakwa (MP) and Pearl Lentsoane (NG) for their leading roles during the pandemic.

Committee meetings

a. NEC meetings (Over the past financial year)

i. 11 March 2022: Hybrid AGM

ii. 14 May 2022: Hybrid NEC meeting

iii. 3 September 2022: Informal meeting held during the PSSA conference

iv. 19 November 2022

v. 18 February 2022

b. Branch AGMs

i. All SAAHIP branches held their AGMs successfully between October and December 2022 as per constitutional requirements. It is pleasing to notice that some branches were supported by the Department of Health in hosting the AGMs. We really appreciate this contribution and partnership.

Membership

The association currently has 2 995 members. Table II shows the distribution of paid members. There is some growth in membership that can also be attributed to the active visibility of our branches through CPDs and other support activities throughout the provinces.

Table II: SAAHIP Membership per branch (30 September 2022)

Branch	Members	Branch	Members
Northern Cape/Free State	149	Southern Gauteng	440
Western Cape	577	Northern Gauteng	254
Mpumalanga	149	KZN Coastal	422
Limpopo	183	KZN Inland	336
Eastern Cape	324	North West	158
Non-resident	3		

Correspondences and invites

a. Gauteng Pharmaceutical Services Annual Conference
We received an invitation to participate and to address the Gauteng Province Pharmaceutical Services Conference on 13 October 2022. I delivered a presentation under the topic: The role of pharmacists post the pandemic and towards NHI.

b. FPD mental health for healthcare workers round table
I participated in the FPD-hosted round table, discussing the causes and effects of mental health for healthcare workers. Strategies to address the scourge of mental health were also discussed. The report for the round table will be released for public consumption once all the work is done.

SAAHIP activities

National projects (focus areas)

Our focus areas have a reference to our strategic plan and the requirements stemming from the nine pillars of the Presidential Health Compact, the NHI Bill and the new Developments for Pharmacy 2030. All branches and members of NEC have been assigned a focus area. Below is a summary of the focus areas:

1. Policies and legislation: NEC (and NG after consultation with branch committee)
2. Membership and Marketing: Eastern Cape
3. Relationships with employers and policy makers: PRESCO and Union liaison committee
4. Conference: Southern Gauteng
5. Communication: North West
6. Compliance with Health System Standards – Limpopo
7. EDL/STG review committee participation: Western Cape
8. National Health Insurance – Working document
9. Human Resources for Health: President and Past President
10. Improved access to essential medicines: KZN Inland
11. Quality and Safety of Health Services: KZN Coastal
12. Governance and Leadership – Mpumalanga and FS/NC

During the past year, there has been very little action on the focus areas that in some way have been attributed to the disruptive impact of the pandemic. The reporting template was updated and all branch Chairpersons and Deputies were trained on the focus areas on 19 November 2022. Taking from the 2019–2022 presidential report, what we want "to achieve from the focus area projects is to ensure that all work that has been tasked to NEC produces quality outcomes which when translated to practice, its impact becomes visible and can be implemented at branch level and at our different workplaces."[1] While the focus areas have been set, one critical aspect in the provision of health that needs to be expressed boldly and innovatively is the digital transformation that is happening in every industry, including health. The Western Cape has shown the lead in the industry's disruptive nature of the fourth industrial revolution (4IR) and how it affects and influences the provision of pharmaceutical services in its broad and narrow terms. This is something that should not be ignored nor feared but embraced and championed by pharmacists for pharmacists. Perhaps it's time to ask, how does SAAHIP lead institutional pharmacy in the realisation of the South African digital health strategy?

Branch activities

I need to express that as a member of SAAHIP, one is proud to see how pharmacists both individually and collectively continue to contribute to leading health and provision of pharmaceutical services. One key highlight is seen during the 2022 Pharmacy Month activities. There has been some direct and indirect contributions of SAAHIP pharmacists in building relationships with different and important stakeholders. The Mpumalanga branch collaborated with the Department of Health during the World Aids Day Symposium and working with the Clinical Care Platform a CPD in ART optimisation and the role of pharmacists in governance. The Limpopo branch's strengthening relationship with the health MEC and collaboration in hosting the African Traditional Medicines Symposium as well as the 1st Limpopo Wound Care Conference is notable. Northern Gauteng partnered with the Pretoria branch of the PSSA, pharmacy students associations from Sefako Makgatho University and TUT on a "HOTDOC and Educate" to promote women and youth health during Pharmacy Month.

Presidential participation at branch level

I would like to draw you to lessons learnt while attending different branch AGMs towards the end of 2022. There is so much drive in the branches, yet there is so much silence. Those who are active in the association are really active and visible, and those who are silent are very silent. Most branches struggle to attract their current active members to the AGMs. I was able to attend the following AGMs:

- Western Cape AGM (26/10/2022): also had a CPD on pharmacy digitisation. The opportunities are an ocean-wide area requiring a new attitude to grab.
- Eastern Cape and KZNC (12/11/2022): in both branches we also talked about the renewal of our efforts to achieve more and to unite towards rebuilding and restrengthening and reminding each other about who SAAHIP is and why we exist.
- Limpopo (25/11/2022): had a full multi-discipline symposium on African traditional medicines and a spotlight was lit on the role of pharmacists in traditional medicines and concomitant use with conventional medicines in managing non-communicable diseases.
- Northern Gauteng (26/11/2022): the conversation was similar to that of Eastern Cape and KZNC.
- Mpumalanga (1/12/2022): had a symposium covering ART optimisation and the role of the pharmacist in ART as well as clinical governance. We also talked about revisiting the reasons we became pharmacists and tried to align our current ambitions with the Basil Statements, the FIP Development Goals and building ourselves as the 10 Star Pharmacist.

- SAPSF (5–7/12/2022: the Northern Gauteng Branch Chairperson was sent to represent SAAHIP and to address the new breed of pharmacists on emerging opportunities in pharmacy and other SAAHIP priorities.
- Branches have held several support workshops for pharmacist interns to help them prepare for the pre-registration exams across the country.

SAAHIP history

During the 2020/2021 committee, a resolution was taken to collect SAAHIP history for future use. This focuses on SAAHIP formation, structures, critical decisions taken over the past years and how they have come along as well as other building blocks that were put together over the years. This is part of *acknowledging* the history of our country and that of our profession and in part *honouring* those who have worked for the development of our profession as enshrined in the preamble of the constitution.[2] Ms Susan Buekes has been very instrumental in collecting the information through a web blog (https://pharmacynibbleshistory.blogspot.com). Although, so far, most of the information comes from the KwaZulu-Natal Region, we would like to appeal to those who have pockets of history to come forth and help us put it together as a reference for future generations of pharmacists.

Constitution training

A two part-training on the application of the SAAHIP constitution was held on 6 and 19 October 2022 and was presented by Andy Gray and Gary Black. It was held virtually and hosted by the PSSA. The training targeted branch committees with the aim of improving participation in matters relating to the constitution as well as branch governance.

CPD on preparation of curriculum vitae for young pharmacist

SAAHIP hosted a once-off session for young pharmacists to help them prepare their CVs in line with the job market on 29 November 2022. The CPD was presented by the PSSA President, and it focused on public sector requirements with principles that overlap with the private sector as well.

Social contribution

SAAHIP continues to support Operation Smile as the main social project. We have been successful in allowing for the creation of many beautiful smiles over the years. This support could not be possible without the support of the branches' leadership and the members of the branches. In 2022, SAAHIP members contributed R44 000 towards Operation Smile, a total of nine smiles.

SAAHIP 2023 conference

The 37th Annual Conference and 66th Annual General Meeting will be held from 9–12 March 2023 at the Champagne Sports Resort, in the Drakensberg. Work is underway to gather sponsors and partners for the conference, a first full-on SAAHIP face-to-face conference. A call for abstract was extended twice due to slow response. The closing date was 22 November 2022.

Structural changes implemented post the pandemic

SAAHIP has stood over the years due to the energy that is drawn from one another. From a meeting point of view, hybrid meetings have been normalised as part of NEC meetings. This saves on cost and time for the association. However, they limit the robust engagement that is needed to gain a strong view on matters as well as build existing ideas to fruition.

Financial support to branches

As part of ongoing improvements for SAAHIP, a finance SOP has been developed as a guide to providing financial support to SAAHIP branches in the future.

Conclusion

I would like to thank Kaajal Chetty for paving a smooth way for me as I occupied this hard seat of leadership in SAAHIP. I also appreciate the support of the NEC and the advice from past presidents and co-opted members of the NEC. We serve with the most talented and committed pharmacists.

We are looking forward to the 2023 conference and many other engagements where SAAHIP will play a part.

The healthcare delivery landscape is ever evolving. There is a need for systems reform, practice adaptation, attitude change and harmonisation of pharmacy practice across the different provinces and sectors. The traditional role of dispensing and supply chain, while being acknowledged as the most visible aspect, there is a need for pharmacists to remind themselves by answering the following questions:

1. What is a pharmacist (this is not for an exam; it is for reminding each other of our identity)?
2. Who are you (as a pharmacist, as a sector or an institution)?
3. How relevant are you given the current health challenges (systematically and clinically)?
4. What is your role?
5. What are our influencers (both internal and external) that serve as core driving forces beneath our wings?

It is in finding answers to these questions and more that will help SAAHIP shape a new paradigm shift to remain relevant. As you join in formulating answers, let us take note from the inspiring words of Jim Rohn who said "*Don't wish that things were easy, wish that you were better*". Stealing from the thoughts of Margaret Mead, "*Never doubt that a small group of thoughtful, committed citizens can change the world; indeed, it's the only thing that ever has*."

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Cum Laude

Academy of Pharmaceutical Sciences

Design and characterisation of a Pluronic-F127-based injectable thermoresponsive intratumoural hydrogel

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[2] Wits Advanced Drug Delivery Platform Research Unit, Department of Pharmacy and Pharmacology, School of Therapeutic Science, Faculty of Health Sciences, University of the Witwatersrand, South Africa

Sandrine Tanga is the winner of the 2022 Young Scientist competition – Laboratory Science category

Abstract

The intravenous administration of chemotherapeutic agents causes an array of side effects during the treatment course, leading to physical and psychological distress. Additionally, these drugs struggle to permeate deep within the tumorous tissue cells which limits their efficacy. Herein, an intratumoral thermoresponsive hydrogel containing Pluronic™ F127 (PF-127) was designed to improve the targeted delivery of oncology drugs to cancer cells. Natural polymers, chitosan (CH) and *k*-carrageenan (*k*CRG), were employed to enhance the rheological, mechanical and erosion properties of the hydrogel system. The hydrogel maintained a liquid state at 4 °C and transitioned to a gel at 31 °C, with adequate mechanical and erosion properties. The results of this study indicate that CH/*k*CRG/PF-127/LIM shows potential as an injectable thermosensitive hydrogel system for administering drugs within solid tumours.

S Afr Pharm J 2023;90(1):41-44

Introduction

Sadrine Tanga

Chemotherapeutics are effective and widely used against cancer, however, their intravenous administration leads to poor permeation and side effects, such as cardiotoxicity, myopathy, nephrotoxicity and immunotoxicity.[1] Several strategies, such as the design of analogues and the use of smart drug delivery systems (DDSs), such as nanoparticles, hydrogels, and liposomes, have been explored to control chemotherapeutic targeting and improve treatment outcomes. Among the smart DDSs used, injectable hydrogels have been widely explored to improve drug targeting in cancer treatment. Hydrogels comprise a 3D polymeric structure which stores drugs within its gel network, allowing for a controlled and slow release. Thermosensitive hydrogels respond to changes in temperature by transitioning from liquid to gel. Thermoresponsive hydrogel delivery systems are advantageous for tumour targeting because they can be modified to maintain therapeutic concentrations of the drug within the tumour site, while providing excellent biocompatibility, degradability, and sustained drug release.[2]

However, thermosensitive hydrogels are often associated with weak mechanical properties which limit their ability to remain at the target site without breakage or collapse resulting from biological interference or design defects.[2] The mechanical strength of a hydrogel system is, therefore, of considerable importance to maintain rigidity and structural integrity within the tumour. Pluronic™ F127 (PF-127) is a common thermosensitive polymer frequently employed for its safety and lower critical solution temperature (LCST) at physiological conditions, however, it demonstrates poor mechanical strength when used alone. Therefore, chitosan (CH) and *k*-carrageenan (*k*CRG) featuring favourable biocompatible properties and mechanical strength were used to improve the mechanical properties of PF-127. The synergic incorporation of these polymers could improve the in vivo stability of thermoresponsive systems, based on their ability to enhance hydrogel mechanical strength in formulations, such as films and wound dressings.[3]

To target the issue of poor drug permeation and accumulation in tumours, limonene (LIM), a natural monoterpene, was selected for its high lipophilicity and chemotherapeutic activity in various

cancers such as breast, lung, and prostate cancer.[4] Doxorubicin (DOX) was used as a model drug to assess the drug-loading efficiency of the system. The present study investigates the crosslinking of CH, *k*CRG, PF-127 and LIM to obtain an injectable thermoresponsive hydrogel for targeted drug delivery applications. The unique approach of this paper is the employment of LIM in the polymer blend to potentially aid DOX diffusion. As such, the formulation could provide sustained drug release and appropriate physicochemical characteristics with improved anticancer activity.

Materials

DOX was purchased from DB Fine Chemicals (Johannesburg, South Africa). LIM and *k*CRG were purchased from Iffect Chemphar Co., Ltd (Hongkong, P.R. China).

Ethanol (96% v/v) was supplied by Laborem (Johannesburg, South Africa). PF-127, CH (medium molecular weight), sodium hydroxide (NaOH), disodium hydrogen phosphate, potassium dihydrogen phosphate and chromatography-grade methanol were obtained from Sigma-Aldrich® (Johannesburg, South Africa). Analytical grade glacial acetic acid was obtained from Saarchem (Pty) Ltd (Johannesburg, South Africa).

Methods

Preparation of thermosensitive hydrogel

CH and *k*CRG solutions were prepared separately according to a method adapted from Pourjavadi and colleagues.[5] Briefly, 10 ml of CH and *k*CRG solutions of 0.3% w/v were prepared by dissolving 300 mg CH in 1% v/v glacial acetic acid, and 300 mg *k*CRG in deionised water heated to 60 ± 2 °C. After mixing for 10 min at 800 rpm, the two solutions were further diluted to 40 ml each. *k*CRG solution was then transferred dropwise (5 ml/min) to the CH solution while vigorously stirring at 1 400 rpm at 50 ± 2 °C. Thereafter, the CH/*k*CRG solution was transferred to a rotary evaporator (50 ± 2 °C) and left to evaporate until the volume was reduced to approximately 10 ml.

For drug loading, 0.0005% w/v DOX solution prepared in 20% v/v ethanol and 0.1% v/v LIM was subsequently added and mixed into the solution. The CH/*k*CRG solution was mixed into the DOX-LIM solution. Thereafter, the CH/*k*CRG/LIM-DOX solution was transferred to an ice water bath, and 15% w/v PF-127 was added to the solution. The polymer blend was stirred until a homogenous, red-coloured solution was obtained. The pH of

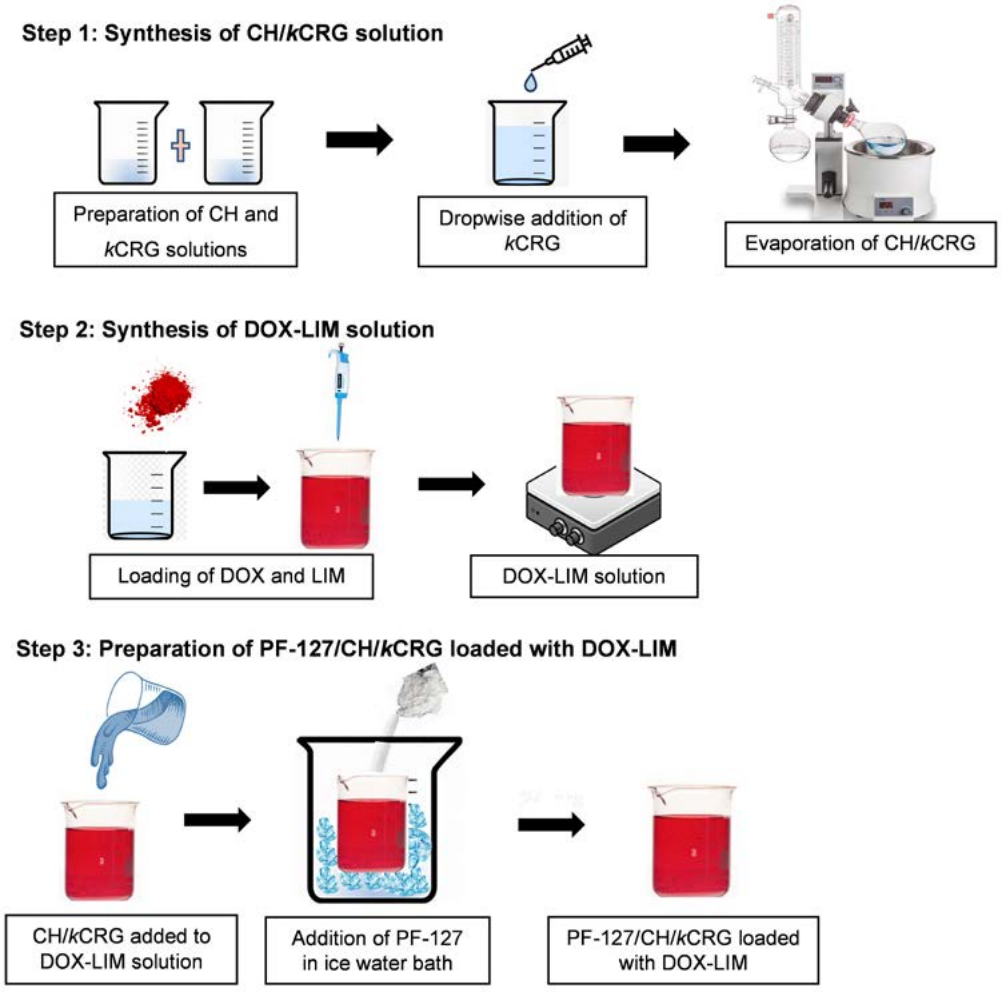

Figure 1: Schematic representing the synthesis of thermoresponsive PF-127/CH/*k*CRG hydrogel with DOX-LIM

the solution was adjusted to approximately 5 using 2 M NaOH. The sample was transferred to a refrigerator at 4 ± 2 °C where it was stored for 24 hours. The synthesis process is depicted in Figure 1.

Fourier transform infrared spectroscopy

The molecular transitions and chemical composition of the hydrogel were confirmed using Fourier transform infrared spectroscopy (FTIR) (Perkin Elmer 400 FTIR) over a wavenumber range of 4 000–650 cm^{-1} for interactions between polymers and excipients.

Thermal analysis

The thermal behaviour of the hydrogels was analysed using thermal gravimetric analysis (TGA) (Perkin Elmer TGA 4 000 thermogravimetric analyser, Waltham, USA). The hydrogel sample was heated at 10 °C/min from 20–600 °C with nitrogen gas at a flow rate of 20 ml/min.

Rheological analysis

The hydrogel sample was analysed using an ElastoSens™ Bio^2 rheometer (Rheolution Inc, Montreal, Canada). Hydrogel samples of 5 ml were analysed for storage modulus and loss modulus over a temperature range of 4–40 °C.

Compressive strength

The compression strength of the hydrogel was measured using a Mecmesin mechanical analyser, Poly Test Instruments (Johannesburg, South Africa). The hydrogel sample (5 ml), placed in a size 6 poly top vial maintained in a water bath at 37 ± 2 °C, was compressed under a load of 20 N, speed of 10 mm/min, and displacement of 5 mm.

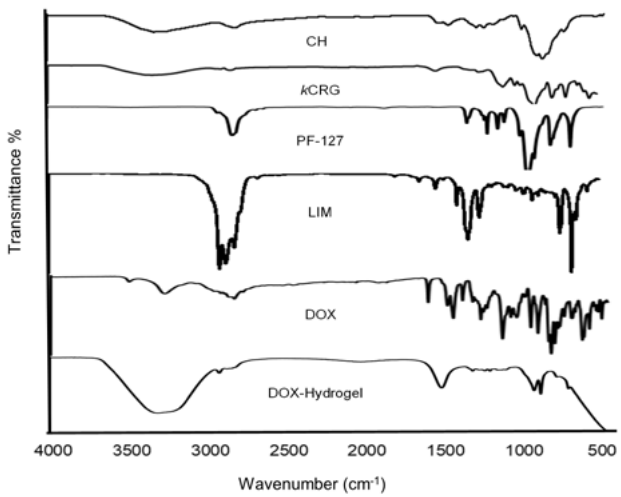

Figure 2: FTIR spectra of hydrogel formulation indicating peak similarities to CH, *k*CRG, PF-127, and LIM

Erosion

Erosion studies were performed over a period of six weeks. A hydrogel mass of 1 g was left to gel in a poly top vial at 37 ± 2 °C. PBS (1 ml, pH 6.8) was then added to the gel. The sample was maintained at 37 ± 2°C and 70 ± 2% RH in a humidity chamber (Labdesign Engineering (Pty) Ltd, South Africa). At weekly intervals, the PBS was removed, the swollen hydrogel was weighed and fresh medium was added to the hydrogel.

Results and discussion

Synthesis of hydrogel

The PF-127/CH/*k*CRG hydrogel was successfully prepared and a red solution was obtained (resulting from the colour of DOX). FTIR revealed the presence of pertinent functional groups of DOX, CH, *k*CRG, PF-127 and LIM crosslinking (Figure 2). In the hydrogel formulation, the broad peak between 3 000–3 800 cm^{-1} is reflective

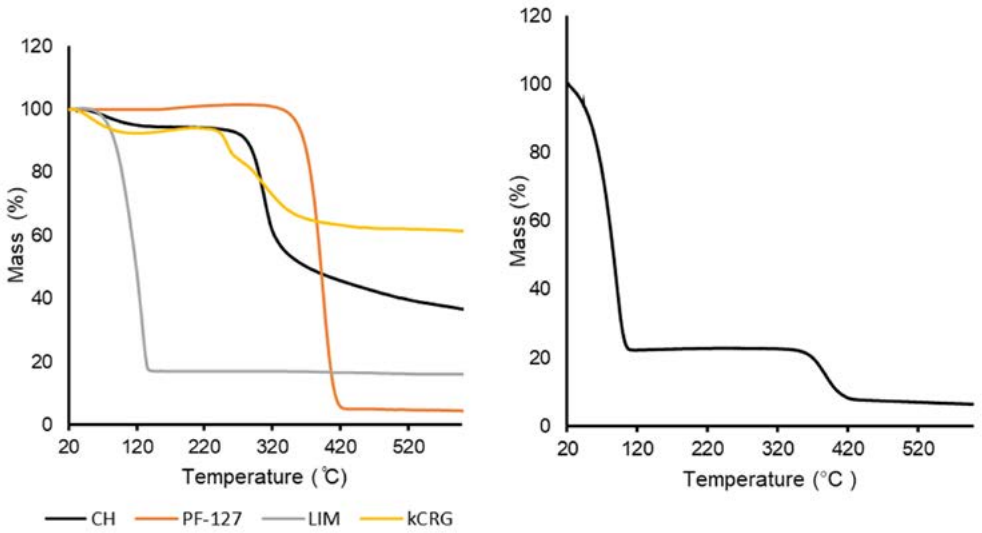

Figure 3: TGA curves of CH, PF-127, *k*CRG, LIM (left) and hydrogel formulation (right)

of the N-H and O-H functional groups in CH, *k*CRG and DOX. The intensity of this peak is significantly increased in the DOX-hydrogel compared to the individual constituents. The increase in intensity is attributed to the electrostatic interaction between the NH_3^+ of CH and OSO_3^- of *k*CRG chains. A similar interaction is observed at the 1 600 cm^{-1} peak due to the C-O and N-H groups of CH and *k*CRG. The small peaks between 2 900–2 800 cm^{-1} and between 900–1 100 cm^{-1}, represent the characteristic alkane and alkene groups in LIM and PF-127, respectively.

Thermal analysis

TGA analysis was performed to assess the thermal stability of the hydrogel formulation (Figure 3). A two-step degradation process was observed from the TGA thermogram, with a mass loss of 20% in the first step due to the evaporation of water and the volatile LIM from the hydrogel network. At 350 °C, the second step occurred with a mass loss of 30% indicating degradation of the polymers. This degradation at high temperatures indicates the extensive crosslinking of the constituents as revealed by FTIR, and high stability over a wide temperature range.

Rheological analysis

Figure 4 shows the rheological behaviour of the hydrogel as temperature increases. Above the LCST (31 °C), PF-127 underwent thermal gelation which increased the storage modulus G′ of the hydrogel network to 1 400 Pa at 37 °C, while the loss modulus G″ (310 Pa at 37 °C) slightly increased due to aggregation of the hydrophobic poly (ethylene oxide) chains of PF-127[4]. The high storage moduli compared to loss moduli with increasing temperature, indicate the elastic nature of the hydrogel. The LCST of 31 °C was reached within three minutes and is favourable for the thermoresponsive design of an injectable formulation, since the system maintains its liquidity at ambient temperature for ease of administration.

Compressive strength

The compressive strength of a system is instrumental in identifying Young's modulus (E), which informs the degree of stiffness of

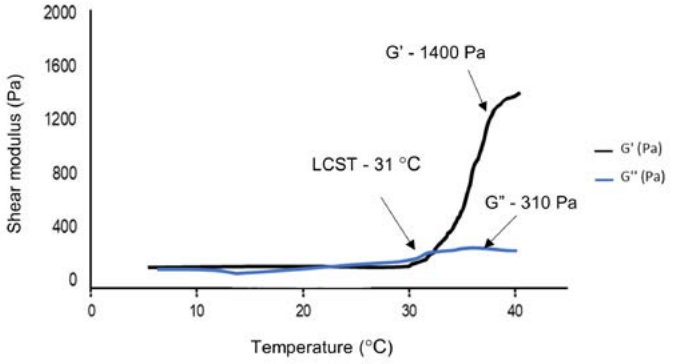

Figure 4: Shear storage (**G′**) and shear loss (**G″**) modulus as a function of temperature (4-40°C) for PF-127-hydrogel

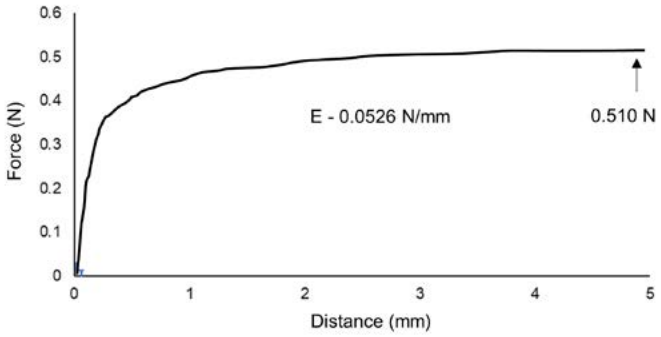

Figure 5: Compression graph indicating the peak force and Young's modulus (E) of PF127-hydrogel (0.3% CH, 0.3% *k*CRG, 15% PF-127, 0.1% LIM) at 37°C

the hydrogel when force is applied lengthwise. As shown in Figure 5, E was 0.0526, and the highest force, obtained at a distance of 5 mm, was 0.510 N which is within the range of tumourous tissue strength (1 000–7 000 Pa).[6] The high force can be attributed to the elasticity and energy-storing ability of the hydrogel, as well as the extensive crosslinking between CH and *k*CRG which stabilises the polymer network.

Erosion

For sustained DOX release, the hydrogel should gradually degrade over time. The thermosensitive hydrogel eroded very slowly in the first week (2.26% mass loss) due to the physical crosslinking of CH and *k*CRG which enhanced mechanical strength and reduced water penetration into the hydrogel network. At five weeks, the hydrogel underwent 75% erosion, thus, showing capacity for long-term drug release.

Conclusion

A thermosensitive PF-127-based hydrogel was designed with sol-gel transition at 31 °C within 3 minutes. Crosslinking of CH, *k*CRG, and PF-127 with LIM was successful, according to FTIR and thermal analysis. The mechanical and rheological profiles show the potential for improved drug accumulation at the tumour site, and the system's erosion of five weeks shows potential for long-term drug release. The thermosensitive hydrogel could serve as a promising strategy for site-specific drug delivery to tumours while reducing side effects.

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Jayne Elizabeth Rishworth

16 October 1978–15 January 2023

My dear friend passed away after a brave battle with cancer. She was an exceptional wife to David, devoted mother to Jonathan and Amelia, and darling daughter of Rev Rob and Gay Penrith.

Jayne was never a person to boast of personal achievements.

She attended Erica Girls' Primary School, where she was head girl in 1991. She then attended Alexander Road High School where she excelled in her studies and music, playing in the band.

Professionally, she completed her internship at Provincial Pharmacy and community service in the Military, after studying at Nelson Mandela University.

I met her when we both started working at the Provincial Hospital Port Elizabeth (PHPE) in 2005. She never raised her voice at a disgruntled patient or staff member. She would inhale deeply, analyse the situation and immediately proceed to find a solution calmly.

After her tenure at PHPE, she worked as a locum at Medi-Rite Pharmacy.

She furthered her career in academia where she assisted with lecturing, oral exams and taking 4th year's on rounds to Dora Nginza Hospital.

In every area of Jayne's career, she was afforded the opportunity to share her light and wisdom. She left everyone with a bright smile and an uncanny gift of making one feel better about oneself.

To say she made a difference in many lives and will be missed is an understatement.

Family, friends, colleagues, students, her dear children, husband and parents were richer for knowing her. Even the ballroom dance floor will miss her enthusiasm.

Jayne's legacy will be the example she set for us all, walking in her Lord's footsteps.

Her concern for others' well-being, despite her physical state of immense pain, will forever be remembered, as she lit up the room with her smile.

Thank you for setting the bar high for us, Jayne.

We aspire to emulate your good deeds, thinking of your contribution at Lake Farm (for intellectually challenged adults).

We will forever be grateful for the impact your life made, quietly and effectively.

Till we meet again, my friend…

Vanessa

Calming the acute

S4 Betadexamine liquid

betamethasone 0,25 mg
dexchlorpheniramine maleate 2,0 mg

is indicated as a second-line therapy when antihistamines are not effective for the treatment of:

- Short-term treatment of allergic rhinitis
- Steroid-responsive dermatological allergies and steroid-responsive dermatoses

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