September/October 2023. Vol 90 No 5
SA Pharmaceutical Journal

sapj

ISSN: 2221-5875

New

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NEW LOOK

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- RUNNY NOSE
- SINUS PRESSURE

3 IN 1

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

S2 OTRIVIN PLUS Nasal Metered-dose Spray (Solution). Each 1 ml contains 0,6 mg of ipratropium bromide and 0,5 mg of xylometazoline hydrochloride. (Preservative-free). Reg. no.: 46/16.1/0819.

Applicant: GlaxoSmithKline Consumer Healthcare South Africa (Pty) Limited, 39 Hawkins Avenue, Epping Industria 1, Cape Town, 7460
Company reg. no.: 2014/173930/07. For full prescribing information refer to the professional information approved by the medicines regulatory authority.

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- South African Association of Community Pharmacist Sector of the PSSA
- SA Association of Hospital and Institutional Pharmacists
- SA Association of Pharmacists in Industry

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S Afr Pharm J 2023 Volume 90 Number 5 (September/October)

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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.

Online submission

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:

1. This manuscript has currently only been submitted to SAPJ and has not been published previously.
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.
4. The submitting/corresponding author is duly authorised to herewith assign copyright to Medical and Pharmaceutical Publications (Pty) Ltd
5. All co-authors have made significant contributions to the manuscript to qualify as co-authors.
6. Ethics committee approval has been obtained for original studies and is clearly stated in the methodology.
7. A conflict of interest statement has been included where appropriate.
8. A title page has been uploaded as a separate supplementary file and the submission adheres to the instructions to authors in terms of all technical aspects of the manuscript.

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Article sections and length

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

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

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

South African Pharmaceutical Journal (SAPJ): Strengthening our interdisciplinary network

Natalie Schellack

We, at the South African Pharmaceutical Journal, owe our remarkable success of publishing the most original and ground-breaking scientific research findings, review papers, and other valuable contributions, to our exceptional authors. Their unwavering dedication and commitment to providing up-to-date content for pharmacists deserve our utmost gratitude.

As we step into 2024, we are excited to announce our plan to appoint discipline-specific assistant editors. These editors will play a crucial role in the peer review of manuscripts, sourcing new authors and reviewers, and offering guidance to the editorial team on the latest trends in pharmacy, specific to South Africa. To ensure a well-rounded and diverse representation of scientific disciplines, we will collaborate with heads of departments from various universities to form an editorial team that reflects both the diversity of the Journal's audience and the fields it serves.

With the increasing number of submissions to SAPJ, we understand the importance of having an adequate number of experts available for timely and thorough reviews.

As the year comes to a close, it is an opportunity for us to reflect on the incredible developments and advancements within the pharmacy practice domain. Health care is constantly evolving, adapting to meet challenges and incorporating the latest breakthroughs. Pharmacy, as a critical component of health care, has played an instrumental role in the administration, education, and equitable distribution of COVID-19 vaccines. Moreover, the implementation of pharmacist-initiated management of antiretroviral therapy (PIMART) has empowered pharmacists to take a more active role in primary care. The recent ruling in favour of PIMART by the North Gauteng High Court signifies the significance and effectiveness of this intervention programme in improving access to HIV and AIDS treatment.

Looking towards the future, we have exciting prospects for leveraging artificial intelligence in the field of pharmacy. Innovations such as machine learning assistance, blockchain traceability, pharmacy automation systems, and E-prescribing hold great potential for implementation in South Africa. While the healthcare sector globally has been perceived to lag behind other industries in the adoption of technology, the South African healthcare technology market presents significant opportunities for growth.

As we move forward, let us embrace collaboration, adaptation, and investment in innovative solutions that prioritise the well-being of patients and ensure equitable access to healthcare services.

Finally, I would like to thank SAPJ members, PSSA, and Medpharm editorial staff for their dedication to the Journal's success.

President's Message

Changing of the Guard – It is "that" time!

Joggie Hattingh
PSSA President

After serving for three terms as President of PSSA it is time to hand over the baton to a new President, who with his new committee, will take the PSSA forward. I will still have the privilege to be part of the Presidential Committee, but in a much different capacity.

Firstly, allow me to congratulate Tshif Rabali on his election as President of the PSSA and Shawn Zeelie on his election as Vice-President and then to Lynette Terblanche who has been an anchor for me during my term, on her re-election as Honorary Treasurer.

May you, with the four sectoral Vice-Presidents, be blessed during your term with integrity and wisdom to take our profession forward!

Remember, there is one thing you can give and still keep… your word! You will encounter many challenges and come across so many pitfalls! Be aware and be alert! There are always two choices: an easy choice, where the only reward is that it's easy, and the difficult choice.

During my tenure as President and the many years on the Presco I was blessed to make so many friends and meet many like-minded pharmacists locally and internationally. I must admit that I hardly remember the challenges I had to face, as the fond memories created and friendships forged by far outweigh any challenge.

It is heartening to see that there are still so many pharmacists who are willing to serve the profession without compensation at branch, sector and national level. This is what enables the growth of the PSSA while some other professional organisations' membership is withering away!

To each pharmacist who worked alongside me in the PSSA over the years, thank you! You all enriched my life and I value your commitment and friendship always.

Then there is another changing of the guard!

After almost 30 years of serving the PSSA as Executive Director, Ivan Kotzé will retire early in 2024. Ivan has served the profession with distinction and led us through so many crises. He did this in such a calm collected and efficient way that most of us never realised that there ever was a crisis and that it was averted! Ivan guided us with integrity and his insight regarding legal matters, the impact of regulations and policy implications are beyond what many legal practicians can offer.

Ivan will be sorely missed at the office, but luckily, he will still avail himself for counsel and guidance when requested!

We are very fortunate to welcome our new Executive Director PSSA: Ms Refiloe Mogale who will officially take office on 1 February 2024.

Refiloe is no stranger to us, as she has been on the PSSA Presidential Committee for many years. Refiloe will bring a new energy and focus to the work of the PSSA. She comes with her own unique set of strengths and will have different priorities, whilst continuing the excellent groundwork laid by her predecessor.

Refiloe also has the full support of her very efficient professional team; Michelle Bernard (COO), Dr Mariet Eksteen, Anri Hornsveld and Nitsa Manolis as well as the full contingent of support staff.

I appeal to each member of the PSSA to give your full support to the newly elected Presidential Committee, National Executive Committee and to the new Executive Director.

Yours in Pharmacy!

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PSSA AGM

The PSSA AGM was held on 14 August 2023. Due to the FIP conference taking place in Cape Town in 2024, a decision had been taken in 2022 not to have a conference in 2023 so the AGM was held virtually.

Executive Director announced

During the AGM it was announced that Ms Refiloe Mogale will be joining the National Office in Pretoria as from 1 February 2024. Refiloe will be the new Executive Director when Ivan Kotzé retires at the end of March 2024. Congratulations to Refiloe, you will move the Society into a new and vibrant era!

Elections

At the AGM a new PSSA Executive Committee for the 2023/2024 year was elected. Congratulations to all members that were elected! The Exco has representatives from all 4 sectors and all branches, so if you would like to find out more or get more involved contact your Exco representative.

Presidential Committee

President	Tshifhiwa Rabali
Deputy President	Shawn Zeelie
Honorary Treasurer	Lynette Terblanche
Immediate Past President	Joggie Hattingh
Vice-President: APSSA	Lorraine Thom
Vice-President: SAACP	Johannes Ravele
Vice-President: SAAHIP	Nhlanhla Mafarafara
Vice-President: SAAPI	Gina Partridge

Branch representatives

Border and Eastern Districts	Kristi Beckermann
Cape Midlands	Alice Lategan
Cape Western Province	Renier Coetzee, Jameel Kariem, Brent Sin-Hidge
Free State	Martlie Mocke-Richter
KwaZulu-Natal Coastal	Mahendra Naidoo, Thandeka Njapha
KwaZulu-Natal Inland	Azraa Bassa
Limpopo	Mohale Seepe
Mpumalanga	Gideon Vosloo
Northern Cape	Danielle Tshabalala
North West	Nico Scheepers
Pretoria	Morné Adamson, Murial Kopanye
Southern Gauteng	Rashmi Gosai, James Meakings, Thanushya Pillaye
Ordinary member	Sham Moodley (KZN Coastal Branch)
Ordinary member	Ntombizodwa Luwaca (Cape Western Province Branch)
Ordinary member	Seshnee Moodley (Border & Eastern Districts Branch)

Fellowship

Fellowship of the Society is to recognise those members who have consistently served to promote the profession and have significantly furthered the aims/objectives of the PSSA during his/her membership in exceptional ways at Branch, Sector and/or National Level over a significant number of years.

This year Fellowship of the PSSA was conferred on Prof Renier Coetzee, Dr Mariet Eksteen, Ms Anri Hornsveld, Dr Nirupa Misra, Mr Johannes Ravele and Prof Ilse Truter.

Honorary Life Membership

Honorary Life Membership was bestowed on Gary Black. Gary Black needs no formal introduction. The resident expert on legal and practice matters, he has been the pride of the Cape Western Province and the country on a whole. Gary's journey with the PSSA began in 1980 when he was elected onto the PSSA CWP Branch committee. He has served continuously on the branch committee on numerous sub-committees and held various portfolios including Student Liaison, Sport/Social Involvement, Constitution, etc. His career as the Director of PSSA CWP has spanned 27 years (October 1995 to October 2022). Always but a call or message away, Mr Black's humble and approachable nature has inspired many around him. A family man by day and one of South Africa's most passionate Pharmacy experts by day too, somehow Gary has managed it all with grace. Now a retiree, he still keeps his passion

alive as a consultant to the PSSA and frequently shares his wisdom through the pages of the SAPJ. With his "Little Black Book" in hand, he remains one of our greatest resources.

Thank you from Gary himself

Thank you!

It is always impossible, on occasions such as this, to thank and name every individual for such a prestigious honour.

However, it would be remiss of me if I did not at least acknowledge some and highlight the role they played in my life as a pharmacist.

Firstly, I grew up in a platteland community pharmacy under the great example of professionalism and service set by my pharmacist Father. So, I developed a love for pharmacy at a very young age.

I got to love pharmacy so much that I married a pharmacist! Without the many sacrifices made by my wife, Anne, I would not have been able to devote the time and energy necessary to pursue my career. Always keeping me in line and providing a shoulder to cry on when I got frustrated and impatient with the Committees!

I was fortunate to work for a great Branch of the Society with a supportive committee and staff that allowed me to pursue and develop my professional interests and be involved in contributing to the National body.

Thanks too to my colleagues at head office for welcoming me into their fold. Special thanks to Ivan for all his support, friendship and patience in tolerating my somewhat exuberant enthusiasm. And of course, thanks to the leadership of the Society over many years for tolerating me!

And now….my own story:

Many know that as a youngster, I was a keen rugby player. At a very young age it became apparent that I was physically built for the job!

One rugby coach drilled the following into my head. He constantly reminded me:

" Black, you are a lock forward which means ***<u>you are a donkey</u>****!*

Your job is to keep your head down, shove forward, bind the scrum together, maul the opposition in the loose scrum, win good clean line-out ball and generally get the ball out to the backline players as quickly as possible for them to score the tries.

YOU ARE A DONKEY *in service of the rest of the team!"*

By the age of about twelve, with my long legs and increasing height, I began to resemble a mule rather than a donkey. But in the eyes of the coach my destiny as a donkey was set and my job for life was clearly determined. My one coach, Meester Apie Lötter, came armed with a "kweperlat" and had no hesitation in using it on our backsides if he felt his donkeys were not getting the job done to his satisfaction.

Having accepted my lot in life as the working donkey on the rugby field, I consoled myself with the realisation that even donkeys had some good qualities such as loyalty, determination, honest hard work, being a good, supportive team mate and never giving up! And certainly not looking for the limelight!

So, I strove to live up to the good traits of a donkey rather than being concerned that, due to my physique, I would never fit into fashionable clothes or a slinky sports car.

But I can proudly say that I started playing 1st team rugby at the age of 15 in grade 10 and played in every game for the next three years until I left school. More importantly, in all those years I only scored one try and that was because, having done the hard (donkey) work in winning the ball and getting it out to the backline, I was following up, caught a good cross kick and crashed over the try-line like a good donkey should! I learned to secretly take great pride in the points scored by my mates Gerry and Dave out on the wing, knowing well that it was us donkeys that made it possible for them to shine.

But even donkeys get old and slow. So, as this old donkey retires to the green pastures of the Deep South, my only hope is that you have been satisfied with my years of service and that the Society continues to grow from strength to strength under new, dynamic leadership.

And, if on reflection you recall my shortcomings, please forgive them because you must remember, some of us donkeys are only human too!

Gary Black

William Paterson award

Dr Natie Finkelstein was awarded the William Paterson award. Natie is undoubtedly one of the most well-known and influential pharmacists in South Africa. His reputation as a lecturer and mentor is legendary amongst generations of his past students and colleagues. However, Natie's influence extends far beyond this. Exercising his passion for pharmacy, superior knowledge, concern for patients, high ethical standards and insistence on both "doing the right things and doing things right" during a career which now extends well beyond 50 years, he has deservedly earned the right to be recognised by the Society as a recipient of the William Paterson Award.

Thank you from Natie himself

I acknowledge with grateful thanks receipt of your congratulatory message on my recent award by the PSSA. It is indeed a major highlight in my long career in the pharmaceutical profession and am still quite bewildered why I was fortunate enough to be so honoured. The "favour" you ask is rather more difficult. I delivered an informal and impromptu acceptance at the virtual AGM and do not have a clue what I had said, as there was no prepared written transcript. My addled memory made a supreme effort to recall the gist of what I had said that morning. I then used those thoughts and moulded them into words that would be coherent and meaningful. I therefore trust that the effort below will succeed

in adequately expressing my gratitude and personal ecstasy as a recipient of the award.

In accepting the signal honour of the highest accolade awarded to a pharmacist by the PSSA, I am humbled not only by the special recognition associated with the award but am also acutely aware that I am standing on the shoulders of other prominent and worthy recipients who have preceded me. Although I am extremely grateful for this prestigious award in my twilight years, it is indeed fitting to dedicate it to the many people who contributed so selflessly to my success, i.e. my devoted spouse and daughters, parents, apprenticeship master, teachers, lecturers, professors, supervisors, students, colleagues and friends.

Over some six decades in the profession, one tends to reflect nostalgically on the many highlights and honours. In this regard, I must pay tribute to the members and staff of the CWP Branch of the PSSA in allowing me to serve in many different capacities and to gain invaluable experience and proficiency in pharmacy matters. The William Paterson Award – rarely awarded – must surely be the ultimate recognition by one's peers and the cherry on top of a fulfilling professional career in pharmacy for the recipient.

I have always been an ardent adherent of service before self and never expected any award for effort in the best interests of the profession, humanity and healthcare. When the reward does arrive somewhat unexpectedly, it does fill one with extreme gratitude and the conscious acknowledgement to our Creator, who in His abundant mercy, has blessed me with longevity and good health to serve our noble profession with dignity, honour and integrity.

Dr Natie Finkelstein

The PSSA/Alpha Pharm distance learning programme 2023

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

Module 4 – Sports supplements in the pharmacy

The use of sports nutrition supplements is widespread at all levels and in all types of sports. Supplements target various aspects related to health and exercise performance. These include:

- Providing energy
- Preventing micronutrient deficiencies
- Maximising recovery
- Maintaining immune function
- Assisting with body composition changes (e.g. fat loss, muscle gain)

Products claiming to enhance exercise performance line the shelves in most modern pharmacies. When used appropriately, supplements can be beneficial for health and sports performance. Unfortunately, the sale and marketing of sports supplements is not well regulated. It is important for the community pharmacist to discern which supplements may benefit athletes, which may have no effect at all, and which may cause harm.

Pharmacists should familiarise themselves with the most common ingredients found in sports supplements. Understanding the function of each ingredient and its potential role in supporting sports performance is fundamental to advising on suitable sports supplements.

There is much misinformation to contend with when dealing with sports nutrition supplements. As a pharmacist, you need to be able to recognise which supplements would be beneficial to an athlete and when and how they should be used.

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

The PSSA/Alpha Pharm clinical education programme 2023 for pharmacy staff

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

Module 4, 2023 – Sports supplements in the pharmacy

The use of sports supplements has become popular amongst both recreational and elite athletes. An athlete is a person taking part in any type of sport or other form of physical exercise. The term athlete is used broadly and does not refer to runners alone.

Athletes generally have higher energy and protein requirements than the general population but have similar vitamin and mineral needs. An athlete's carbohydrate, protein and fluid requirements depend on the type of exercise they do.

Products claiming to improve exercise performance line the shelves in most modern pharmacies. When used appropriately, supplements can be beneficial for health and sports performance. Understanding the function of each ingredient and its potential role in supporting sports performance is crucial.

This module will enable you as the Front Shop Staff member to:

- Recognise and understand the importance of nutrition for exercise performance.
- Understand the role and use of carbohydrates, protein, and fats in sports nutrition.
- Have a basic understanding of the role of key vitamins and minerals for health and exercise.
- Recognise the role of fluids and electrolytes in sport.
- Understand the function of ergogenic (performance-enhancing) aids in sport.
- Be able to give general recommendations on supplements/products based on individual requirements of the sportsperson/person engaging in physical exercise.

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

Watch, listen, and DO something

Watch, listen, and DO something -

The healthcare space is dynamic and constantly changing. What one learnt five years ago in their Bachelor of Pharmacy or Pharmaceutical Sciences degree is probably outdated or has evolved. Some laws have been phased out, some have been introduced; some problems have been solved, some are still escalating and more are developing. Whilst this may make many feel uncomfortable, the truth is that things always need to be changing for growth to occur. Whether the change is rapid or snail-like, it *needs* to happen. If the butterfly does not break out of its cocoon, it will never be able to fly and we will never be able to appreciate its beauty. The same principle applies to most, if not everything in life.

As young pharmacists living in the era of the NHI, PIMART, prescribing nurses, etc., we need to keep watch, listen (for understanding) and DO something when the call reaches our doorstep. This generation must vehemently refuse to fall victim to becoming the custodian that knows and participates in no more than the daily procedures at work that we can easily perform in our sleep. Our call to you today is to scratch around, constantly watch, listen to what is being said and not said and do something when the call comes to act!

Introducing the 2023/24 Steering Committee: a dynamic team ready to ignite the pharmacy world!

We are thrilled to unveil the exceptional individuals who will be leading the charge for the Young Pharmacists' Group (YPG) in the upcoming year. Brace yourselves for an electrifying journey as we introduce our highly talented and passionate team members, each bringing their unique expertise to propel the YPG to new heights of excellence!

Ntombizodwa Luwaca

Ntombizodwa Luwaca – Chair

Leading the way with boundless enthusiasm and a visionary mind-set, Ntombi takes the helm as our esteemed Steering Committee Chair. With her extensive experience in pharmacy practice and leadership, Ntombi brings a refreshingly innovative approach to steer the YPG towards even greater achievements. Get ready for an exhilarating year of transformative initiatives under her guidance!

Luyanda Khumalo

Luyanda Khumalo – Project Coordinator

Prepare to be dazzled by Luyanda Khumalo, our dynamic and resourceful Project Coordinator. Armed with a knack for organisation and an unwavering commitment to excellence, Luyanda is poised to orchestrate a series of ground-breaking projects that will shape the future of pharmacy. Brace yourselves for a wave of innovation and impactful initiatives that will leave a lasting impression on our profession!

Sibusiso Israel Mahlangu – Public Relations Officer

With his infectious energy and outstanding communication skills, Sibusiso Israel Mahlangu assumes the vital role of Public Relations Officer. Sibusiso possesses a true gift for networking and community engagement, ensuring that the YPG's voice reaches far and wide. Be prepared for a whirlwind of

captivating events, engaging content, and meaningful collaborations that will captivate the entire pharmacy world!

We look forward to engaging with young pharmacists this year and making life-long and meaningful connections. Join our inclusive community to enhance your professional development, collaborate with peers, and drive innovation in pharmacy. Let's ignite the pharmacy world together! Stay tuned for upcoming events, webinars, and networking opportunities tailored to young pharmacists like you.

Sibusiso Israel Mahlangu

Professional Innovation Project 2023 Winner

Congratulations to Lili Marie Flax, the recipient of the 2023 PIP grant! Her research project titled: The Organisational Readiness of KZN clinics to implement new TPT guidelines.

"I am deeply grateful to the YPG committee for selecting me for this honour. I am extremely excited, as this money paves the way for my PhD research. As a pharmacist, my passion for public health has been shaped by first-hand experiences in the under-resourced South African public sector. This grant not only supports my academic aspirations but also reaffirms the oath I took to *'to serve humanity'*." – *L.M. Flax*

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!

Current controversies on generic substitution in the transplant community

M Leuschner, N De Beer, N Shellack

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

Corresponding author, email: machel.leuschner@up.ac.za

Abstract

For drugs with a narrow therapeutic index (NTI) like tacrolimus, small changes in dosage can lead to significant changes in blood levels, which can affect both the effectiveness of the drug and the risk of adverse effects. Monitoring is crucial to ensure that the drug is maintained within the desired therapeutic range. Too low levels could lead to organ rejection, while too high levels could lead to toxicity, which can damage the kidneys, liver, and other organs.

When it comes to medications with a NTI, like tacrolimus, the issue of generic substitution becomes more complex. Due to the NTI, small variations in drug concentration can lead to significant differences in clinical outcomes. Generic drugs must be proven to be bioequivalent to the brand-name drug, which means they should have similar bioavailability (rate and extent of drug absorption) when administered under the same conditions.

It's important for individuals taking tacrolimus to communicate closely with their pharmacists, adhere to their prescribed dosage, attend all recommended follow-up appointments, and report any unusual symptoms or side effects promptly.

Keywords: tacrolimus, narrow therapeutic index, generic drugs

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Introduction

The transplant community is currently divided on whether substituting generic immunosuppressants is appropriate for recipients of organ transplants. In order to mitigate the risk of graft rejection and loss following organ transplantation, recipients of transplants require access to immunosuppressive medications (ISMs). The costs associated with ISMs can present a significant burden for transplant patients, potentially restricting access and leading to non-adherence.[1,2] The utilisation of therapeutically equivalent generic alternatives has the potential to alleviate the financial strain on both the public healthcare sector and the private sector, which is supported by medical aid in South Africa. A retrospective study conducted in the USA addressed this issue, utilising data from the Scientific Registry of Transplant Recipients spanning from 1987 to 2013.[3] The primary aim was to assess the financial implications of generic substitution of transplant medications compared to the innovator medicine. This investigation included tacrolimus, administered in kidney, liver, and heart transplant cases. The study revealed substantial cost savings with regards to tacrolimus treatment, ranging from 48% to 67% in overall per-patient expenditures. Additionally, transplant recipients managed to save between 63% and 79% of their out-of-pocket expenses.[3] Despite ongoing debates within the transplant community, uncertainties persist regarding the substitution of generic products for brand-name ISMs, as well as the interchangeability of different generic formulations.[4] Tacrolimus is a medication that belongs to a class of drugs known as calcineurin inhibitors. It is commonly used in the field of organ transplantation to prevent the rejection of transplanted organs. Tacrolimus works by suppressing the immune system's response, which helps prevent the body from attacking and rejecting the transplanted organ. However, due to its mechanism of action and the potential for serious side-effects, tacrolimus is known to have a narrow therapeutic index (NTI).[5] This review aims to define characteristics of narrow therapeutic index medicines and elucidate the stricter regulatory requirements of the US Food and Drug Administration (FDA) and the European Medicine Agency (EMA) for the registration of generic medicines regarded as NTI medicines. In addition, alignment of the South African Regulatory Authority with these guidelines will also be discussed.

Narrow therapeutic index medicines and their characteristics

Defining NTI

There is no clear consensus on the definition for NTI medicines. Regulatory authorities have different definitions based on the characteristics for these medicines. The FDA defines it in terms of medicines with a narrow therapeutic ratio, where there *"is a less than a 2-fold difference in the median lethal dose (LD50) and the median effective dose (ED50) values, or a less than 2-fold difference in the minimum toxic concentrations (MTC) and the minimum effective concentrations (MEC) in the blood".* This demonstrates the importance of individualised dose titration and therapeutic drug monitoring (TDM) to ensure patient safety and efficacy of medicines. The Canadian Health Protection Bureau provides a more clinically practical definition as: *"a less than 2-fold difference in the ratio between the lowest concentration at which the clinical toxicity commonly occurs to the median concentration providing a therapeutic effect."*[6] From a clinical pharmacology perspective this is simply illustrated by the dose response curve. For NTI

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medicines there is a narrow range between the concentration that is therapeutically effective and the concentration that leads to adverse events and toxicity or, on the other hand, therapeutic failure.

Characteristics of NTI medicines

Lists of NTIs are difficult to find in literature, but there is a web-enabled database called "Drug Bank" that provides a list of most medicines with a NTI. These include: aminoglycosides, monoclonal antibodies, ciclosporin, carbamazepine, digoxin, flecainide, lithium, phenytoin, phenobarbital, rifampicin, theophylline and warfarin.[7] Yu et al. summarised five common characteristics of NTIs:[8] (i) NTIs exhibit low intra-individual pharmacokinetic and pharmacodynamic variability but significant inter-individual variability; (ii) Therapeutic dosages should be individualised which requires ongoing therapeutic drug monitoring; (iii) Even a minor dose adjustment could result in a substantial change in the dose response; (iv) Dosage must be titrated in small increments and requires oversight by the attending physician; (v) Serious therapeutic failure could result from sub-therapeutic dosing, which is detrimental to transplant patients as it can lead to organ transplant rejection.[9] In addition, generic alternatives of NTIs must meet stricter bioequivalence criteria than other multisource medicines.

Bioequivalence, quality standards and generic interchangeability of NTIs

A generic medicine is manufactured to be the same as an already marketed brand-name medicine in dosage form, safety, strength, route of administration, quality, performance characteristics, and intended use. These similarities help to demonstrate bioequivalence, which means that a generic medicine works in the same way and provides the same clinical benefit as the brand-name medicine. Due to the greater risk of therapeutic failure or adverse effects, both the FDA and the EMA have implemented stricter bioequivalence criteria for the registration of generic equivalents of NTIs.[8,10]

Regulatory requirements for bioequivalence in NTIs

At the 2011 FDA Advisory Committee for Pharmaceutical Science and Clinical Pharmacology meeting, the regulations on establishing bioequivalence between a NTI generic and the originator were updated to a stricter limit of 10% difference in blood concentration between the originator and the generic (this relates to a range between 90.00–111.11% (note 111.11 = 1/0.9) instead of the 20% difference allowed for other generic medicines where the range limits are between 80–125% (where 125 = 1/0.8).[2,11] These regulations followed on those implemented by EMA in 2010.[2] The proposed study design to determine bioequivalence between the generic NTI and its originator is a four-way, fully replicated, crossover study in healthy subjects to compare the mean and inter-individual variability between the formulations.[8] Typically, participants are divided into four groups, each experiencing a different order of treatments, and repeating each treatment sequence with multiple participants. This design is aimed at minimising the impact of order effects and individual variability, making the results more robust and credible. A two-by-two study design is also used where one half of the group receives the originator medicine first, followed by a washout period, and then the generic medicine and vice versa for the other group. Pharmacokinetic data is gathered for the two groups and the ratio of the geometric mean value for the experimental formulation to the mean value for the standard formulation is determined for both C_{max} and AUC. Bioequivalence is demonstrated when the mean ratio's 90% confidence interval (CI) falls within a predefined range.[12]

SAHPRA guideline and regulatory requirements for biostudies of NTI medicines

To demonstrate its commitment to align with global best practices, the South African Health Products Regulatory Authority (SAHPRA) has taken an executive decision to harmonise specific policies and procedures with those of the EMA, which, in turn, is in alignment with the International Council for Harmonisation (ICH) technical requirements for medicine registration. The latest version of the SAHPRA Quality and Bioequivalence Guideline was published on the 23rd of May 2023 (found online at https://www.sahpra.org.za/document/quality-and-bioequivalence/), and includes the stricter acceptance limit for NTI APIs of a 10% difference for AUC and C_{max}, where maximum concentration is important for the safety and efficacy. SAHPRA further recognise the WHO, the FDA and other regulatory authorities for guidance when applicable.

Tacrolimus overview and the role of the pharmacist in generic substitution

Tacrolimus pharmacology

Tacrolimus, also known as FK506, is a potent immunosuppressive agent indicated for prevention of organ transplant rejection and treating conditions like atopic eczema and inflammatory eye diseases.[13-16] It is derived from *Streptomyces tsukubensis*.[17] The mechanism of action involves binding to a protein named FK506 binding protein (FKBP), leading to the inhibition of calcineurin's phosphatase activity. This enzyme, calcineurin, normally dephosphorylates the nuclear factor of activated T cells (NF-AT), a transcription factor responsible for promoting the production of IL2 and other inflammatory cytokines. By obstructing calcineurin's function, tacrolimus hinders the transcription of IL2 and other T lymphocyte cytokines.[18] Tacrolimus further enhance the actions of glucocorticoids and progesterone by binding to FKBPs inside the hormone receptor complex.[19] Since its introduction into the market in 1994 tacrolimus has been the cornerstone of immunosuppression after solid organ transplant for the prophylaxis of organ rejection. In South Africa it is indicated as primary immunosuppression in liver and kidney transplant patients and as a "rescue: therapy for heart allograft rejection.[20]

Table I: Bioequivalence studies for tacrolimus

Comparator		*n*	Patient population	Outcome	Ref.
2012 Sandoz	Randomised crossover PK of generic vs. reference	71	Intent to treat kidney transplant patients (60% Caucasian males)	Similar PK profile in kidney transplant patients	21
2011 Sandoz	Single-centre, retrospective, nonrandomised study	103	Liver or kidney transplant patients switched from originator to generic	Trough concentrations declined by average 1.98 ng/mL in liver and 0.87 ng/mL in kidney. No rejection.	22
2014 Sandoz	Prospective evaluation of systematically switching transplant recipients to generic tacrolimus	67	Kidney transplant patients (62% Caucasian males)	Generic tacrolimus statistically bioequivalent to the reference but individual patient monitoring essential	23
2010 Sandoz	Prospective, observational trial conducted at four transplant centers	70	kidney (*n* = 37), liver (*n* = 28), or multiorgan (*n* = 5) transplant patients included African American population	Tacrolimus dose requirement and trough concentrations were similar with branded and generic. Note: three times as many patients underwent dose changes after conversion to the generic	24
2013 Teva	Single-centre, prospective, randomised, cross-over, open label, steady-state bioequivalence study	35	Elderly kidney transplant patients at steady state using the originator medicine	Significantly higher systemic tacrolimus exposure with generic in elderly patients	26
2013 Sandoz	Single-centre comparison of the clinical outcomes at six months	99	Renal transplant recipients	Comparable clinical outcomes at six months in patients receiving either originator or generic from the time of renal transplantation	27
2014 Sandoz and Dr Reddy	Prospective, replicate dosing, partially blinded, randomised, 3-treatment, 6-period crossover bioequivalence study	71	Kidney (*n* = 35) or liver transplant (*n* = 36) patients	Bioequivalence (average and scaled average) criteria met between originator and two generics and between generics in kidney or liver transplant patients	25

Tacrolimus bioequivalence studies

Generic substitution in South Africa is well established to curb healthcare costs and increase accessibility to life-saving medicine. But, economic drivers should never overshadow the welfare of patients. Tacrolimus is classified as a NTI medicine and is therefore subjected to undergo *in vivo* bioequivalence studies in accordance with the FDA and EMA guidelines using the stricter criteria of a 90% confidence interval. In August 2009, the US FDA approved the first generic formulation of tacrolimus and since then a number of bioequivalence studies within the transplant patient population have been conducted (Table I). Most studies concluded that the generic tacrolimus can be safely substituted for the originator tacrolimus, and one study also found bioequivalence between two generics of tacrolimus.[21-25] These findings were however gathered in controlled clinical settings and the importance of therapeutic medicine monitoring was highlighted in all the studies and especially in elderly patients where bioequivalence could not be established.[26]

Bioequivalence studies are usually conducted in first-world countries, and not much is known about African population groups. A ten-year, single-centre longitudinal cohort study of kidney recipients, conducted between 2005 and 2015, found that the intra-patient variability in the African-American population puts them at a high risk of acute rejection.[28] Therefore, it is reassuring to know that SAHPRA has adopted the stricter bioequivalence regulations of EMA. Furthermore, the SAHPRA-approved tacrolimus prolonged-release formulations contain a bolded warning stating that these generics are not interchangeable with the immediate-release formulations of tacrolimus, unless careful monitoring and supervision by a transplant specialist (PI) is available.

Tacrolimus adverse events[29,30]

Dermatological reactions might include conditions like acne vulgaris, alopecia, pruritis, and rash. In terms of endocrine and metabolical impacts, there could be changes in serum bicarbonate and iron levels, and even the development of new-onset diabetes mellitus after transplantation (NODAT). The medication might also lead to various metabolical imbalances such as hypercalcaemia, hyperkalaemia, hyperlipidaemia, and more. Gastrointestinal adverse events include symptoms like abdominal pain, nausea, vomiting, and diarrhoea. The genitourinary system might be affected by an increased risk of urinary tract infections. Hepatic function tests could show abnormal results due to the medication. Tacrolimus might augment susceptibility to infections, including bacterial infections and viruses like the BK virus, cytomegalovirus, and others. Neuromuscular and skeletal effects might be felt as arthralgia and muscle cramps. In the realm of vision, there could be blurred vision and other visual disturbances. Ears might experience otalgia, otitis media, and tinnitus due to tacrolimus. Renal effects could include acute renal failure, increased blood urea nitrogen (BUN), elevated serum creatinine (SCr), and other kidney-related issues. Overall, tacrolimus has a wide range of potential effects on various systems in the body.

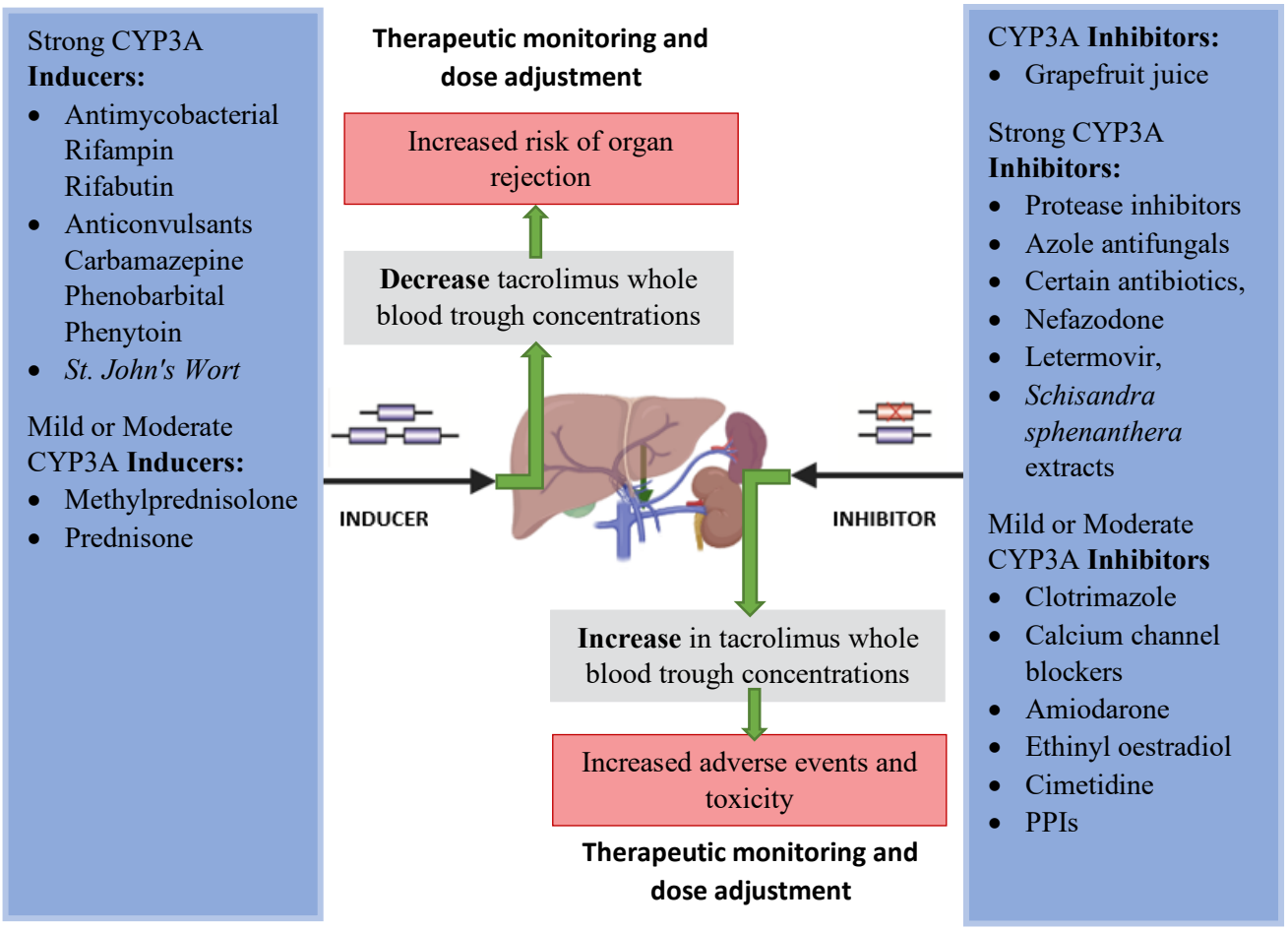

Figure 1: The influence of CYP3A inhibitors and inducers on the tacrolimus treated liver or kidney transplant patient

Drug interactions with tacrolimus[31]

Clinical and laboratory parameters should be carefully monitored during therapy with tacrolimus to prevent potential pharmacokinetic and pharmacodynamic medicine interactions. Concomitant administration of tacrolimus with inhibitors or inducers of both the Cytochrome P450 (CYP)3A metabolising enzymes and enteric multi-drug efflux transporter, P-glycoprotein, affect the blood concentration of tacrolimus.[32] Knowledge of these frequent medicine interactions is important, as they could result in therapeutic failure and acute organ rejection or toxicity due to over-exposure of tacrolimus (Figure 1). Some of the most frequent medicine interactions are given in Table II.

The pharmacist and dispensing NTIs

To reduce the potential for error, tacrolimus should be prescribed with a full description of the drug and the brand. If the brand, strength and dose frequency are not clearly stated on the prescription, the dispensing pharmacist should check with the prescriber to ensure the appropriate medicine is dispensed. A prospective, replicate dosing, partially blinded, randomised, 3-treatment, 6-period crossover bioequivalence study found that tacrolimus and two tested generic products were bioequivalent in individuals with a kidney or liver transplant.[25] The authors concluded that bioequivalence data in transplant patients were similar to that in healthy patients. Moreover, the two generic medicines evaluated in the trial were bioequivalent to each other with the tighter FDA SCABE criteria met, and there seemed to be no difference between the different tacrolimus products in terms of within-subject variability.[25] Regardless of this, studies in the genetically variable South African cohort is lacking and switching between different brands of tacrolimus requires careful therapeutic monitoring under the supervision of a transplant specialist.

The pharmacist and tacrolimus

Pharmacists play a critical role in ensuring the safe and effective use of medications with a NTI like tacrolimus. Their expertise in medication management, dosing, drug interactions, and patient education is invaluable in helping patients achieve optimal outcomes while minimising the risk of adverse effects.

Key ways in which pharmacists are involved in managing medications with a NTI like tacrolimus:

- *Dispensing and counselling:* Pharmacists ensure that patients receive the correct medication, dosage, and instructions for use. For medications with a NTI, they might provide additional counselling to patients about the importance of adhering to the prescribed dosing regimen and attending regular follow-up appointments for monitoring.

Table II: Frequent medicine-to-food and medicine-to-medicine interactions

Pharmacokinetic interactions			
PK parameter	**Interacting medicine or food**	**Effect on tacrolimus blood concentration**	**Therapeutic effect and dosage recommendations**
CYP3A Inhibitor	Grapefruit or Grapefruit Juice	Increase in tacrolimus whole blood trough concentrations.	Elevated risk of severe adverse reactions such as neurotoxicity and QT prolongation. Avoid grapefruit.
Strong CYP3A Inducers	Antimycobacterial (e.g. rifampin, rifabutin), anticonvulsants (e.g. phenytoin, carbamazepine, and phenobarbital), and St. John's Wort	Decrease tacrolimus whole blood trough concentrations, thereby increasing the risk of organ rejection.	In response, it is recommended to increase the dose of tacrolimus and regularly monitor tacrolimus whole blood trough concentrations.
Strong CYP3A Inhibitors:	Protease inhibitors (e.g. nelfinavir, telaprevir, boceprevir, ritonavir), azole antifungals (e.g. voriconazole, posaconazole, itraconazole, ketoconazole), certain antibiotics, nefazodone, letermovir, and Schisandra sphenanthera extracts	Raise tacrolimus whole blood trough concentrations. This heightens the risk of serious adverse reactions, including neurotoxicity and QT prolongation.	In cases where these inhibitors are used, it is recommended to reduce the dose of tacrolimus, with specific adjustments for voriconazole and posaconazole. Close monitoring of tacrolimus levels, starting within a few days and continuing as needed, is crucial.
Mild or Moderate CYP3A Inhibitors	Clotrimazole, certain antibiotics (e.g. erythromycin, fluconazole), calcium channel blockers, amiodarone, danazol, ethinyl oestradiol, cimetidine, lansoprazole, and omeprazole	Elevate tacrolimus whole blood trough concentrations, increasing the risk of severe adverse reactions.	To address this, regular monitoring of tacrolimus levels is recommended, along with potential dose adjustment for tacrolimus.
Other Drugs:	Magnesium and aluminium hydroxide antacids, as well as metoclopramide	Potential to increase tacrolimus whole blood trough concentrations and consequently heighten the risk of severe adverse reactions.	Regular monitoring of tacrolimus levels and possible dose adjustment of tacrolimus may be necessary.
Mild or Moderate CYP3A Inducers:	Substances like methylprednisolone and prednisone	Lower tacrolimus concentrations.	To manage this interaction, continuous monitoring of tacrolimus whole blood trough concentrations is advised, with possible adjustments to the dose of tacrolimus if required.
Pharmacodynamic medicine interactions			
Other nephrotoxic medicines	Nonsteroidal anti-inflammatory drugs, antibiotics and chemotherapeutic agents as well as ACE inhibitors	Increased nephrotoxicity with co-administration of tacrolimus.	
Tacrolimus can also aggravate the neurotoxicity of medicines such as ganciclovir.			

- *Dosage adjustment and monitoring:* Pharmacists work closely with healthcare providers to monitor patients' medication therapy. They might be involved in adjusting the dosage of tacrolimus based on the patient's response, laboratory test results, and potential drug interactions. Regular monitoring of blood levels of tacrolimus is crucial to ensure that it remains within the therapeutic range.
- *Medication reviews:* Pharmacists can conduct comprehensive reviews of a patient's medication profile to identify potential interactions or contraindications that could impact the use of tacrolimus. They can collaborate with healthcare providers to make necessary adjustments.
- *Patient education:* Pharmacists provide patients with information about the importance of taking tacrolimus consistently and as directed. They can explain potential side-effects, interactions with other medications, and the significance of regular blood tests to monitor drug levels.
- *Medication management plans:* In collaboration with healthcare providers, pharmacists can help develop medication management plans tailored to the patient's needs. This might include strategies for managing other health conditions or medications that could interact with tacrolimus.
- *Communication:* Pharmacists facilitate communication between patients and healthcare providers. They can address patients' questions, relay concerns to the medical team, and ensure that everyone involved in the patient's care is on the same page.
- *Generic substitution considerations:* If there are concerns about switching between brand-name and generic versions of tacrolimus, pharmacists can provide information about the regulatory standards for generic drugs and how they apply to NTI medications.
- *Adverse event reporting:* If a patient experiences adverse effects related to tacrolimus, pharmacists can assist in reporting these events to the appropriate channels to ensure patient safety and contribute to monitoring drug safety on a broader scale.

Conclusion

Therapeutic medicine monitoring is essential to ensure optimal patient outcomes and to prevent toxicity and possible organ rejection. This is especially important in vulnerable patient groups

including patients on polypharmacy at high risk of medicine interactions, or patients with hepatic and renal failure. The pharmacist should be able to inform patients about the possible adverse effects and medicine or food related interactions.

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An overview of allergic conjunctivitis

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Abstract

Allergic diseases affect many people across the globe. They significantly impact on the quality of life of the people who are affected, creating personal and economic predicaments. Some of the most commonly diagnosed allergic diseases include atopic dermatitis, rhinitis, allergic conjunctivitis and sinusitis. Allergic conjunctivitis is an allergic disease characterised by the inflammation of the conjunctiva caused by airborne allergens; it presents as itching, excessive lacrimation, discharge and pink eye. Usually it is associated with other allergic conditions such as allergic rhinitis and bronchial asthma. Allergic conjunctivitis is further divided into acute, seasonal allergic conjunctivitis (SAC), and perennial allergic conjunctivitis (PAC). Other conditions, such as eosinophilic oesophagitis, are on the rise and are being diagnosed across all continents except Africa. The diagnosis is primarily clinical. Antihistamines have been the mainstay of therapy for most allergic conditions, except for other conditions that require corticosteroids, or in severe allergic conditions such as anaphylaxis where antihistamines are ineffective as main therapy. It is important to consider first- versus second-generation options when treating allergic diseases, also bearing in mind the duration of therapy and any comorbid conditions that a patient might have. This article provides an overview of these conditions and their current management options.

Keywords: allergic disease, antihistamine, anaphylaxis, atopy, atopic march, rhinitis, sinusitis

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Introduction

Allergic diseases are complex diseases caused by a combination of genetic and environmental factors. Allergic diseases are on the increase, affecting approximately 30% to 40% of the world's population. They decrease quality of life and may have an immense influence on personal, social, and economic costs.[1]

An allergic response is a hypersensitivity reaction mediated by the adaptive immune system. The presence of a trigger, such as an allergen or antigen, induces a humoral immunological response, which in turn initiates a complex immunological reaction. This dysregulation in the immune function elevates the plasma levels of immunoglobulin E (IgE). The release of IgE is followed by binding to the allergen or antigen, which in turn stimulates the mast cells to degranulate and release several pro-inflammatory substances that include histamine, chemokines and numerous cytokines.[2]

There are many different factors that come into play when searching for the causative agent of an allergy. Environmental influences that occur in pregnancy and early childhood can alter the physiological, immune, structural and behavioural development of an individual and thus, transform response patterns that influence susceptibility to future diseases.[3] Genetics also play a vital role in the susceptibility of an individual to an allergic disease. The most common allergic conditions around the world include atopic dermatitis, rhinitis, asthma, rhinosinusitis, allergic conjunctivitis and, most recently, allergic oesophagitis.[3,4] Allergic conjunctivitis is primarily a condition that affects young adults, with the average age of onset being 20 years. The symptoms, however, decrease with age.[5]

The atopic march

Atopy refers to the increased sensitivity of IgE to a specific antigen, which in turn, results in a hypersensitive response upon exposure toward the specific allergen in question.[6] 'Atopic march' is a term that refers to the development of various atopic diseases that may develop during childhood. The atopic march may also refer to how the sequence of clinical symptoms and atopic disease manifest during childhood growth and development.[7] The initial development of atopy has been linked to various predisposing risk factors. These include a genetic predisposition, decreased exposure to infections and endotoxins, postnatal antibiotic use, obesity, tobacco smoke, air pollutants, exposure to allergens, maternal weight gain or obesity, gestational use of antibiotics and maternal stress.[8]

Pathophysiology of atopy

There is vast evidence that shows that T-lymphocytes play a major role in allergic diseases. The T-helper cell type 1 (T_h1)/T-helper cell type 2 (T_h2) paradigm has been extensively studied and seems to be the major pathological pathway in allergic diseases. The paradigm explains the relationship between the T_h1 and T_h2 subsets of the T-lymphocyte. T_h1 and T_h2 subsets tend to differentiate from $CD4^+$-naïve T-lymphocytes. This means that whenever a raised response towards either the T_h1 or the T_h2 subset occurs, the other will be reduced.[9] When there is a reduction in T_h1 production, there are observed decreased levels of interferon gamma (IFN-g), interleukin (IL)-2 and tumour necrosis factor (TNF)-beta. This in turn leads to elevated levels of T_h2 effect, owing to a decrease in IgG production, which inhibits T_h2 formation.[9,10] There are various risk factors that can predispose a patient towards the development of atopy. Refer to Figure 2.

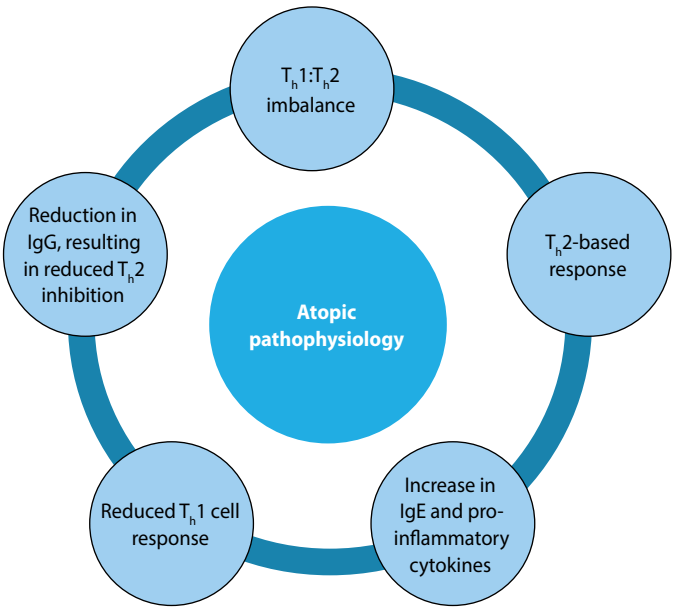

Figure 1: The imbalance between T_h1 and T_h2
IgG – immunoglobulin G, T_h1 – T-helper cell type 1, T_h2 – T-helper cell type 2

Figure 1 illustrates the imbalance in T_h1 and T_h2 that leads to atopic diseases.[10]

The role of histamine in allergy

Histamine is an endogenous substance synthesised from histidine. It has the ability to elicit autacoid effects within peripheral tissues and also acts as a neurotransmitter within the central nervous system (CNS).[11] The role of histamine in the inflammatory process remains significant in understanding the pathophysiology thereof.

The release of histamine in peripheral tissue areas is mediated by mast cell degranulation. This degranulation can be triggered in various ways. In allergic diseases, an interaction between IgE (immunoglobulin E) antibodies and suitable IgE antigens (i.e. the formation of antigen-antibody complexes) that causes allergic reactions (localised histamine release) or anaphylaxis (systemic histamine release), seems to be the major trigger.[11]

There are currently four identified histaminergic receptor subtypes (i.e. the H_1- to H_4-receptors). The H_1-receptor is the main active subtype in mediating acute allergic reactions. There are different effects that may be induced by H_1-receptor stimulation. Some of these effects lead to allergic conditions, which include allergic rhinitis and conjunctivitis, urticaria, pruritus and angioneurotic oedema.[11]

Stimulation of these receptors is also responsible for the vasodilatation and the increased vascular (capillary) permeability that accompanies allergic reactions and inflammation – erythema and oedema, including potentially fatal glottis oedema. Understanding histamine regulation assists in the type of treatment to be initiated in various allergic reactions. For instance, histamine is released systemically in anaphylaxis but the use of an antihistamine alone is not effective in treating anaphylaxis.

Genetic predisposition

Allergies tend to be familial, with patients who suffer from an allergy tending to have an increased risk of having children with some form of atopy.[2] There is vast evidence that shows that T-lymphocytes play a major role in allergic diseases. Several studies have looked at the role of genetics in allergic diseases.

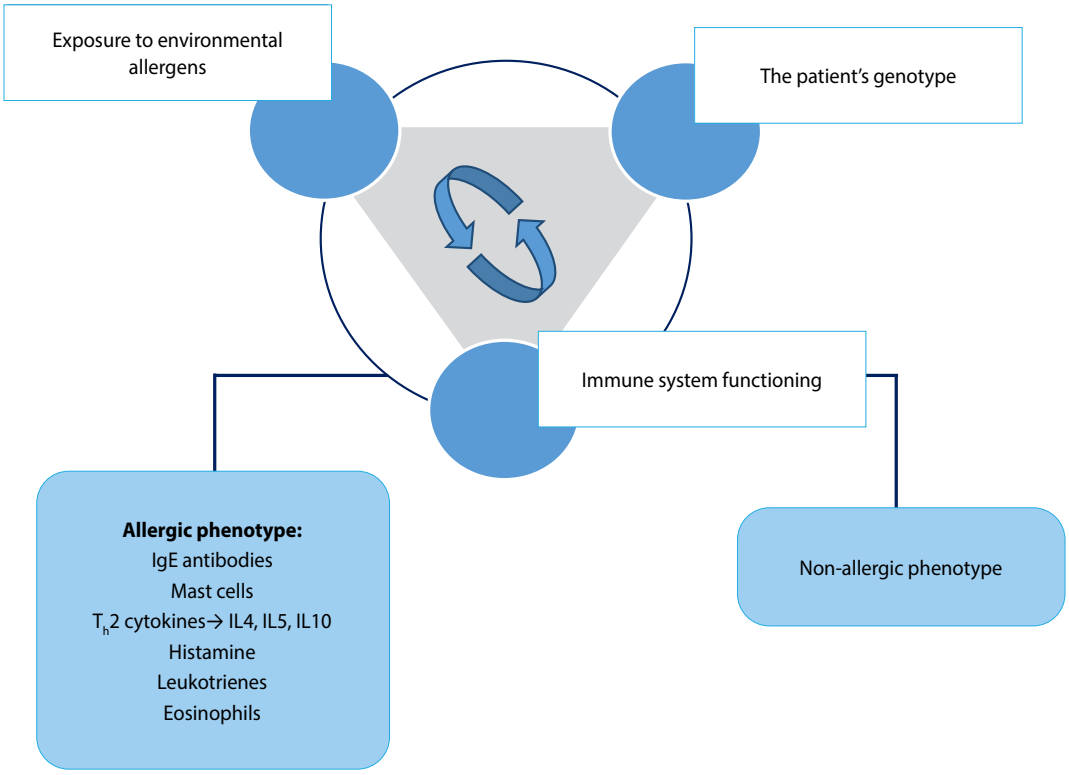

Figure 2: Risk factors for developing atopy[2]

Some studies have had mitochondrial RNA (miRNA) as the main focus of such investigations. The earlier studies have shown that several types of miRNA augment the sensitivity of T-cells to peptide antigens. Evidence suggests that inhibition of miR-181a expression in immature T-cells significantly decreases sensitivity to antigens and enhances the impairment of T-cell selection. T-cell apoptosis is crucial in regulating both the length and strength of T-cell responses. MiR-21 has also been extensively studied, showing significant upregulation during T-cell activation and plays a role in the suppression of apoptosis in activated T-cells. It is therefore essential to understand the role of various miRNA in T-cell regulation as the development of polarised T_H cells is central to the pathogenesis of allergic inflammation because allergic inflammation is predominately a T_H2 response.[12]

Allergen exposure

Exposure to an allergen in individuals with an atopic disease increases the risk of developing a hypersensitivity reaction, regardless of the level of antigen exposure. The evidence showing that immune sensitisation is not dependent on the level of allergen exposure gives credibility towards a belief that the existence of atopic disease is hereditary. On the other hand, low levels of allergen exposure are not sufficient to produce a response, while high levels of allergen exposure induce tolerance toward that allergen, i.e. desensitising it.[13]

Infections and endotoxin exposure

The hygiene hypothesis is applied in most atopic diseases. It predicts that the prevalence of atopic diseases is decreased when a child is exposed to more infectious agents. It is estimated that the exposure to animals, viruses, bacteria and various endotoxins makes children less likely to develop an atopic disease. The hygiene hypothesis emerges from the understanding that bacterial, viral and endotoxin factors trigger an immune response of T_h1 lymphocytes. T_h1 lymphocytes increase the production of IgG antibodies. T_h1 (through IgG) indirectly suppresses the activity of T_h2 which mediates the release of various cytokines including IgE. These T_h2 cytokines are common culprits in the development of allergic diseases.[2,7,14,15]

Intestinal flora

The presence of microbes in the walls of the intestinal tract helps to regulate an immune response. Exposure to microbial flora within the gastrointestinal tract early in life allows for a change in the T_h1:T_h2 cytokine balance, favouring a T_h1 cell response. A shift in the microbial balance initiates a change in immune response.[2] The evidence then suggests that exposure to high dosages of antibiotics in early neonates may alter the composition of intestinal flora, leaning towards an immune response with elevated levels of T_h2. The elevated T_h2 leads to increased IgE production and therefore the likelihood of developing an atopic disease.[16]

Common allergic diseases across the globe

Several allergic conditions are described in more detail below.

Rhinitis

Rhinitis is an inflammation of the nasal mucosa. According to the Australasian Society of Clinical Immunology and Allergy (ASCIA) there are various causes of rhinitis which include: allergies (hay fever), increased sensitivity to irritants such as smoke, temperature changes or the overuse of decongestant nasal sprays.[17] The most common antigens for allergic rhinitis are inhaled allergens, the most concerning being dust mites, animal dander and pollen.[17,18]

Allergic rhinitis (AR) affects approximately 20% of the world population and is considered to be the most common chronic disease.[19] AR is a type 1 allergic disease which reduces quality of life depending on the severity.[20] Exposure to nasal allergens stimulates an IgE-mediated type 1 hypersensitivity reaction, resulting in symptomatic reactions to the allergen. The early characteristic symptoms of allergic rhinitis are rhinorrhoea, nasal congestion and sneezing.[19-21] AR can also be associated with various conditions such as bronchial asthma, allergic conjunctivitis, rhinosinusitis and others.[21]

The inhalation of nasal antigens in sensitised individuals causes the antigens to pass through mucosal epithelial cells, binding to IgE antibodies on mast cells distributed over the nasal mucosa. The antigen-antibody complex stimulates an IgE-mast-cell-mediated early-phase response.[19] Chemical mediators, such as histamine and peptide leukotrienes (LTs), are released from mast cells. The release of these mediators causes irritation to the sensory nerve endings and mucosal blood vessels, leading to early phase reaction symptoms (i.e. sneezing, watery rhinorrhoea, and nasal mucosal swelling).[20] The early phase symptoms usually appear within 30 minutes after exposure to an allergen. Late-phase response results in tissue damage and remodelling, appearing 24 hours after allergen exposure.

The presence of an antigen in the nasal mucosa leads to the stimulation of cytokines, chemical mediators and chemokines which respond by releasing various inflammatory cells, such as activated eosinophils which infiltrate the nasal mucosa. Leukotrienes produced by these inflammatory cells cause nasal mucosal swelling.[19,20]

Sinusitis

Sinusitis is defined as inflammation of the paranasal sinus mucosa. Sinusitis has been replaced with the more correct term 'rhinosinusitis'.[22] The term rhinosinusitis is given preference over sinusitis because sinusitis, in most instances, is almost always followed by inflammation of the adjacent nasal mucosa. The classification of rhinosinusitis is usually based on whether it is acute rhinosinusitis (ARS) or chronic rhinosinusitis (CRS). Many scientists concur on the duration of CRS being longer than 12 weeks while ARS still has different duration classifications from different scientists but usually less than 12 weeks.[23]

Acute rhinosinusitis

ARS occurs as a result of inflammation of the nasal mucosa mainly due to bacterial, fungal, or viral infections, as well as allergies

or exposure to inhaled irritants.[24] It is essential to properly diagnostically distinguish bacterial ARS from viral ARS, to assist with the treatment plan. Treatment in bacterial ARS involves antibiotics which would be inappropriate if used for viral ARS.[23,24]

Chronic rhinosinusitis

CRS affects about 10–15% of the adult population in industrialised countries such as Europe and the US, and is one of the most reported chronic conditions.[25] It has been observed over the years that there are multiple variants of CRS which include characterisation of the disease by chronic infection, non-eosinophilic inflammation, chronic hyperplastic eosinophilic sinusitis (CHES), aspirin-exacerbated respiratory disease and allergic fungal sinusitis.[26] When there is chronic inflammation in the nasal mucosa, the observed result is mucosal swelling (including polyposis), increased mucus secretion, airway obstruction, and blocked sinus drainage. The inability of the nose to eliminate bacteria, viruses, fungi and allergens creates an environment of chronic inflammation which then results in a chronic nasal disease.[24] Some patients with chronic sinusitis present with massive submucosal eosinophilic infiltration. Eosinophilic sinusitis is characterised by multiple nasal polyps, viscous rhinorrhoea, and olfactory disorder, and is often complicated by asthma. Eosinophilic sinusitis is extremely intractable and resistant to surgery, resulting in repeated relapses. Oral corticosteroid therapy often results in a complete response.[20]

Allergic rhinosinusitis

The presence of an allergen can cause inflammation of the sinus mucosa, which may be acute or even chronic. This inflammation prevents the usual clearance of bacteria from the sinus cavity, increasing the chances of developing secondary bacterial sinusitis. It is estimated that more than 50% of people with allergic rhinosinusitis have clinical or radiographic evidence of CRS. About 25–58% of people with rhinosinusitis have some form of inhaled allergen sensitisation. This is confirmed by the presence of raised IgE, which leads to an active immune response. Evidence supports the suggestion that CRS could be an atopic disease driven by IgE sensitisation to aeroallergens.[26] The symptoms of allergic rhinosinusitis include: rhinorrhoea, nasal congestion, facial pain, fever, cough, sore throat and fatigue.[27] These symptoms significantly reduce the quality of life of individuals, creating inconvenience for both people and the economy.

Atopic dermatitis

Atopic dermatitis (AD) is one of the most common chronic inflammatory disorders of the skin with a strong link to genetic predisposing factors. It affects approximately 20% of children and 1–3% of adults in industrial countries.[28] There is a clearly identified hyper-proliferative cutaneous disorder in AD that is associated with a defective skin barrier and a mixed T_H1/T_H2 inflammatory response. This exposes the skin and makes it susceptible to cutaneous infections and moderate to severe pruritus.[12] A major number of patients suffering from AD have been observed to have elevated serum levels of total IgE and allergen-specific IgE, with approximately 50% of individuals testing positive on an atopy patch test.[28] There are several allergens that lead to the exacerbation of AD which may include airborne pathogens, e.g. pollen, and various foods. Avoidance of identified allergens usually has significant benefit to patients with AD.[6,28]

Table I: Potential causes of conjunctivitis[30,31]

Conjunctivitis				
Infectious	**Causative agent**	**Type of discharge**	**Ocular symptoms**	**Accompanying symptoms**
Viral	Adenoviruses (most common cause)	• Watery	• Red eye	Pharyngoconjunctival fever • High fever • Pharyngitis • Enlargement of the periauricular lymph nodes • Bilateral conjunctivitis Keratoconjunctivitis (severe) • Oedema of the sclera • Hyperaemia
Bacterial	*H. influenzae** *S. pneumoniae** *S. epidermidis* *S. viridans* *S. aureus* *Moraxella catarrhalis** *Neisseria gonorrhoeae*	• Mucopurulent/purulent	• Red eye • Oedema of the sclera • Pain in the eye	• Swelling of the eyelid • Mattering and sticking together of the eyelids in the morning
Non-infectious				
Allergic	Allergens (pollen, animal dander)	• Watery	• Red eye • Itching • Burning sensation • Conjunctival oedema	• Swelling of the eyelid • Runny nose • Blurry vision

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RAPID RELIEF FROM OCULAR ALLERGIES[1,2]

References: 1. Spersallerg® Sterile Eye Drops approved package insert, February 1975. **2.** Wertheimer R, Bleßmann G. Antazoline/tetryzoline in comparison with levocabastine eyedrops in acute allergic conjunctivitis. Klin Monbl Augenheilkd. 1997;210(2):93-96.

S2 Spersallerg® Sterile Eye Drops. Each 1 ml contains: antazoline hydrochloride 0,5 mg; tetryzoline hydrochloride 0,4 mg. Ref. No. H1283 (Act 101/1965). Under license from Novartis Pharma AG, Hettlingen, Switzerland. For full prescribing information refer to the professional information approved by the medicines regulatory authority (February 1975).

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Eosinophilic oesophagitis

Eosinophilic oesophagitis is an allergic condition that has recently emerged and has been reported in all continents except Africa.[12] Observed inflammation of the oesophagus with abnormal eosinophils in allergic reaction are the main characteristics of the disease. Potential allergens include cross-reacting molecules, which are common between pollen antigens or latex food allergens. The emergence and prevalence of this disease is becoming a global concern and requires more investigation.[1,12,20]

Allergic conjunctivitis

Allergic conjunctivitis is an inflammatory response of the conjunctivae to allergens such as pollens, environmental antigens (e.g. dust), and animal dander.[29] Hyperaemic conjunctivitis is a common type of conjunctivitis; most patients show symptoms of ocular itching, lacrimation, hyperaemia, eye discharge, etc. Severe symptoms cause eyelid swelling. A number of conditions may present with conjunctivitis (red eye), but it would be best to try and differentiate allergic conjunctivitis from other eye conditions. Knowledge of eye conditions, how they present and their prevalence is important. Before a likely diagnosis is made the following should be considered: the causative agent involved, types of discharge, ocular symptoms and lastly, other accompanying symptoms (Table I).[30]

Types of allergic conjunctivitis

Allergic conjunctivitis can be differentiated into three types: acute allergic conjunctivitis, seasonal allergic conjunctivitis (SAC), and perennial allergic conjunctivitis (PAC). The differences between these three types are listed in Table II.[5]

The role of the pharmacist in the management of allergic conjunctivitis

Pharmacists are exposed to a lot of patients that report acute allergic conjunctivitis and they are the first healthcare professionals that patients approach. Pharmacists should be able to assess patients individually and follow a stepwise approach. They also play an important role in facilitating the selection of artificial tear solutions, ensuring that the solutions are preservative free, suggesting topical antihistamine-decongestant products and oral antihistamines. The pharmacist also provides information or counsels patients on palliative care, such as avoiding allergens and the appropriate storage of medicine, i.e. the refrigeration of topical solutions.[32] Ultimately, referral may be necessary when patients present with comorbidities, symptoms that overlap with other conditions, no response to over-the-counter treatment, contact lens users, severe signs and symptoms.[33,34]

Emerging therapies for allergic conjunctivitis

Topical combination of antihistamine/mast cell stabilisers, i.e. olopatadine, provides an additional, immediate relief benefit as well as the long-term relief from the mast cell stabilisation. This combination also has the additional advantage of once-daily dosing. There is a recognised need for medications that demonstrate rapid onset and a prolonged duration of action. The 24-hour dosing provides maintenance during symptomatic periods without any exposure to preservatives because of fewer instillations. It also promotes compliance. A higher concentration of olopatadine (antihistamine/mast cell stabiliser) is the newest combination therapy.[35] Olopatadine, when compared to sodium cromoglycate, showed that the more expensive olopatadine had fewer patient return visits.[5] Bepotastine, prescription-only drops administered twice daily, has a very high specificity for the H_1-receptor, meaning that it is specific for the ocular itch experienced in allergic conjunctivitis. It also has additive effects on nasal congestion, rhinorrhoea, nasal itching and ear or palate itching.[36]

Asthma

Asthma is one of the most common chronic inflammatory diseases that affect both children and adults. The inflammatory process causes hyper-responsiveness in the bronchial tree, with reversible airflow obstruction. Inflammation of the bronchial tree may result in airway constriction via smooth muscle contraction, the hyper-secretion of mucus, bronchial hyper-responsiveness, and additional narrowing of the airway due to mucosal oedema and sloughing of the epithelial cells.[12]

Allergic asthma is observed to be the most common type of asthma, caused mainly by inhaled allergens, inducing an immune system response.[12] The implementation of therapy must be done

Table II: Differences between the three types of allergic conjunctivitis[5]

Type of allergic conjuctivits	Onset	Causes	Allergens
Acute allergic conjunctivitis	Sudden onset, develops rapidly (within 30 mins) and resolves immediately in the absence of the allergen (within 24 hours)	Environmental exposure	
SAC	Progressive onset and occurs gradually over days to weeks	Specific allergen	• Tree pollen in spring • Grass pollen in summer • Wood pollen in late summer or autumn
PAC	It is mild and chronic and can either increase or decrease in severity	Year-round environmental exposure	• Dust mites • Animal dander • Moulds

after accurate classification of asthma severity. This assists in reviewing the management of the condition when periodic assessment for asthma control has been established. Diagnosing asthma is based on two tools viz. identification of a characteristic pattern of respiratory symptoms and expiratory airflow limitation; these differ for each patient.[37]

Management of allergic conjuctivitis

Allergic diseases can be strategically managed both non-pharmacologically and pharmacologically.[38] The use of pharmacological preparations is usually preferred for use when non-pharmacological methods prove ineffective or insufficient in alleviating the allergic symptoms. Different pharmaceutical preparations (systemic, intranasal, topical, etc.) are used depending on the symptoms and type of allergic disease.[29,38]

Topical therapy is either made up of combination drugs such as an antihistamine and a vasoconstrictor, or antihistamine with mast cell stabilising properties. The former are found over-the-counter, the vasoconstrictor targeting the ocular redness and the antihistamine targeting the allergic symptoms. An example is the tetryzoline/antazoline combination; however, it may cause increased redness for several days after use.[5] The latter have a dual mechanism of action; they block histamine receptors and they also stabilise mast cells and inhibit their degranulation which in turn limits the release of histamine, tryptase and prostaglandin D_2. They also have an effect on leukocyte activity. These drugs are dosed twice daily and as prophylaxis they require two weeks of therapy to reach their maximum effect. Antihistamines with mast cell stabilising properties can cause burning, stinging and irritation, headaches or ocular dryness when instilling the eye drops and these adverse effects can be avoided by refrigerating the drops.[5]

Local vs systemic antihistamines in the treatment of allergic conjunctivitis

The results of randomised trials indicate that topical medications are more effective when compared to oral therapies when used for ocular conditions.[5] The systemic use of antihistamine only partially relieves ocular allergic symptoms[32] and patients may also experience systemic adverse effects such as drowsiness and dry mouth.[34] Therefore, topical administration especially of a combination (antihistamine/decongestant) is more effective for ocular allergic symptoms. However, in the situation where oral therapy is used, the second-generation antihistamines are preferred as they cause less sedation because of their reduced ability to cross the blood–brain barrier.[32,33]

Local decongestants

Local decongestants are mainly sympathomimetic drugs that stimulate α_1-adrenergic receptors producing vasoconstriction. This in turn decreases mucosal oedema and local vasodilation.[38] Examples of the most commonly used drugs include xylometazoline, phenylephrine and oxymetazoline.[39] Local decongestants are usually indicated to reduce acute symptoms as prolonged use can produce undesirable effects to the user.[38] After persistent use (usually more than five days), rebound rhinitis and conjunctivitis medicamentosa start to appear. Oxymetazoline and xylometazoline have a long-acting effect on the α_1-receptor, whereas phenylephrine has a shorter duration of action, lasting up to approximately four hours.[40] The mechanisms of action of the local decongestants illustrated in Figure 3 involve targeting the vasodilatation of the mucosal oedema (i) that causes nasal congestion; (ii) the molecules of a suitable nasal decongestant bind to, and stimulate adrenergic alpha 1-receptors; (iii) resulting in vasoconstriction, therefore alleviating the mucosal oedema, and increasing the diameter of the nasal lumen.

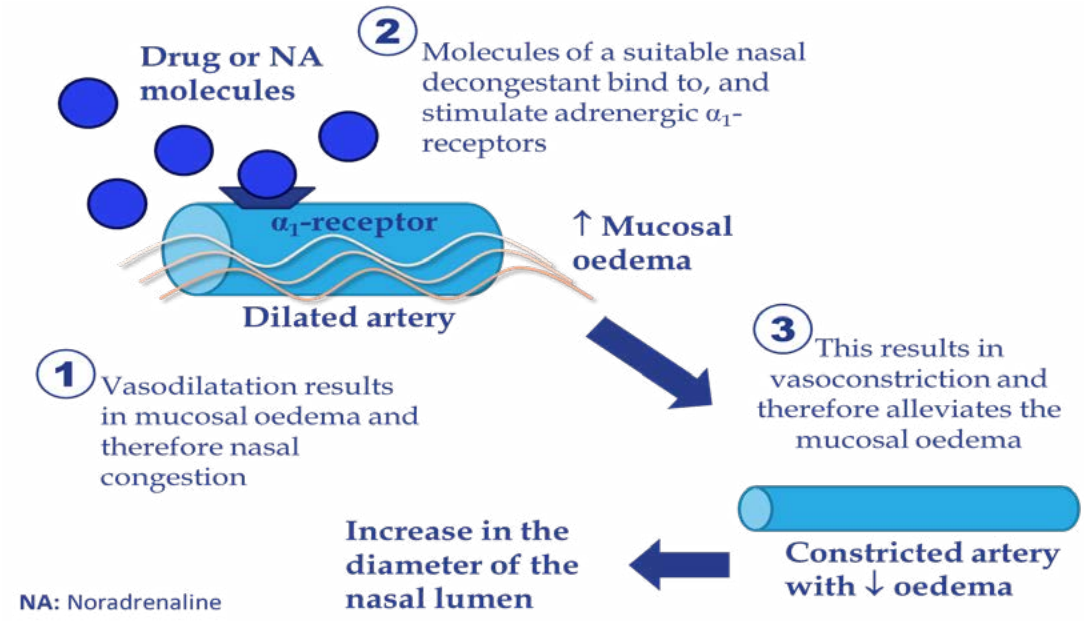

Figure 3: The mechanisms of action of local decongestants

Systemic decongestants

These agents stimulate α_1-receptors producing vasoconstriction, reducing oedema, redness and itching. Their preparations usually contain an antihistamine. It is important to note that combination therapy of a systemic decongestant and an older-type H_1-antihistamine can produce drowsiness and a lack of motor coordination. Systemic decongestants available in South Africa include pseudoephedrine, phenylpropanolamine and phenylephrine. The use of phenylpropanolamine has produced sub-arachnoid bleeding with haemorrhagic stroke in women using it as an appetite suppressant. The total daily dosage of phenylpropanolamine should not exceed a 100 mg.[38]

Corticosteroids

Glucocorticosteroids can be used for various allergic conditions such as asthma, allergic rhinitis and with minimal use in allergic conjunctivitis. They exert their pharmacological action by modifying protein synthesis through regulating transcription, and indirectly by modifying the activity or half-life of transcription factors and mRNA. The currently available intranasal corticosteroids include: beclomethasone, budesonide, fluticasone, mometasone, triamcinolone and ciclesonide. The newer agents, namely mometasone, fluticasone, and ciclesonide, are also administered intranasally and result in minimal systemic effects.[39] The most common local side-effects experienced with the intranasal corticosteroids include dryness, stinging, burning, and epistaxis. Chronic use of topical corticosteroids may lead to atrophy of the nasal mucosa. It is therefore advisable to use these agents for the shortest time possible to prevent unpleasant adverse effects associated with long-term use.[41] Systemic corticosteroids such as hydrocortisone and prednisone can be used in chronic dermatitis to reduce the frequency of allergic flares.[28]

Table III: The differences between first- and second-generation antihistamines[43]

	Older, first-generation H_1-antihistamines	Newer, second-generation H_1-antihistamines
Drug examples	Promethazine Chlorpheniramine Dexchlorpheniramine Hydroxyzine Cyclizine	Cetirizine and levocetirizine Loratadine Ebastine Fexofenadine Mizolastine Rupatadine
Frequency	Usually administered in 3–4 daily dosages.	Usually administered once or twice a day.
Mechanism of action	Potent blockers of H_1, α_1 and muscarinic receptors.	Selective H_1-receptor antagonists.
Blood–brain barrier	Cross the blood–brain barrier (lipophilicity, low molecular weight and lack of recognition by the p-glycoprotein efflux pump).	Generally, do not cross the blood–brain barrier at recommended dosages (lipophobicity, high molecular weight and recognition by the p-glycoprotein efflux pump).
Indications	Chlorpheniramine displays lower levels of sedation than many of the other examples in this group, and may therefore be better suited to the management of allergic reactions.	Rupatadine fumarate is approved for the treatment of allergic rhinitis and chronic urticaria for adults and children aged 12 years and older.
	The options for sedation include hydroxyzine, promethazine and diphenhydramine. However, more suitable agents may be used in the management of insomnia.	Fexofenadine has the shortest half-life of the systemic agents. Furthermore, it also does not display any H_1-receptor occupancy inside the central nervous system at therapeutic dosages.
	As an antiemetic agent, choose from cyclizine (*syn.* meclizine), diphenhydramine, hydroxyzine or promethazine, for example. First-generation H_1-antihistamines may be very useful in the management of postoperative nausea and vomiting, as well as vertigo.	Cetirizine has the greatest likelihood of displaying some degree of H_1-receptor occupancy inside the central nervous system, which may result in some level of sedation, albeit at higher-than-recommended dosages.
Side-effects	Potentially cause side-effects, such as: Sedation Drowsiness and dizziness Hyperactivity (meta-reaction) Insomnia Convulsions Impaired driving performance Fatigue and lassitude (well documented)	Do not cause relevant side-effects (sedation, fatigue, hyperactivity and convulsions) in the absence of drug interactions.
	Anticholinergic side-effects, including a dry mouth, urinary retention, gastrointestinal upset and appetite stimulation.	Minor side-effects include: Nausea Light headedness Drowsiness Headaches Agitation and a dry mouth
Toxicity	Case reports of toxicity are regularly published.	There have been no reports of serious toxicity.
Overdose	A lethal dosage has been identified in infants and young children.	Do not cause fatality in overdose.

The H_1-antihistamines

H_1-antihistamines based on pharmacological classification are grouped into different generations. This system of classification is based on their target receptors as well as side-effect profile.[42] The H_1-antihistamines are classified into first-generation (older, sedating, multi-potent blockers) and second-generation (non-sedating, newer) antihistamines. First-generation antihistamines include promethazine, chlorpheniramine, dexchlorpheniramine and cyclizine whilst the second-generation antihistamines include cetirizine (and levocetirizine), loratadine, ebastine, fexofenadine and mizolastine. The most significant difference (refer to Table III) between the two classes is that first-generation H_1-antihistamines have the ability to cross the blood–brain barrier and the second-generation non-sedating H_1-antihistamines have very limited ability, if none at all, to cross the blood–brain barrier. It is also important to note that two generations of systemic (oral and/or parenteral) agents, topical (including intranasal and ophthalmic) H_1-antihistamines are available as well.[11,18,40]

First-generation H_1-antihistamines

These older H_1-receptor blockers have been shown to have sedative and multi-potent receptor-blocking abilities. Their ability to cross the blood–brain barrier distinguishes them from the newer generation H_1-antihistamines. The chemical structure of the first-generation antihistamines permits them to have a certain degree of non-selectivity, exerting antagonistic effects of an antimuscarinic or anticholinergic, antihistaminergic, α_1-adrenergic blocking, anti-serotonergic and local anaesthetic nature. Because of their wide range of receptor blocking, the first-generation H_1-antihistamines have a variety of indications and uses, which range from allergies and rhinoconjunctivitis, to nausea and vomiting, motion sickness and insomnia. Their effects on multiple receptors, on the other hand, also have undesirable effects (refer to Table IV) and are not recommended for use in patients who suffer from glaucoma, benign prostatic hyperplasia and in cardiac patients (i.e. ischaemic heart disease, myocardial infarction and congestive heart failure).[43]

Table IV: The adverse effects of first-generation antihistamines, as reflected by receptor activity[44]

Receptor antagonistic interaction	Side-effects
Histamine$_1$ receptor	A reduction in central nervous system neurotransmission, sedation, reduced cognitive and neuro-psychomotor performance, and an increased appetite.
Muscarinic receptor	Xerostomia, urinary retention and sinusoidal tachycardia.
α-adrenergic receptor	QTc-interval prolongation and ventricular arrhythmias.
Serotonergic receptor	An increased appetite.
IKr and other cardiac channels receptors	QTc-interval prolongation and ventricular arrhythmias.

The following drugs in this group are of note:

- The options include hydroxyzine, promethazine and diphenhydramine. These drugs are used in the management of insomnia but there are more suitable agents that may be used.
- Cyclizine (*syn.* meclizine), diphenhydramine, hydroxyzine or promethazine, are examples of antiemetic agents. First-generation H_1-antihistamines may be very useful in the management of postoperative nausea and vomiting, as well as vertigo.
- Chlorpheniramine is better suited for use in allergic reactions due to its relatively lower sedation levels than the other first-generation antihistamines.

It should be noted that these "older" drugs have never been optimally investigated and profiled from a clinical pharmacology perspective.

Second-generation H_1-antihistamines

Second-generation H_1-antihistamines are relatively newer antihistamines that do not possess the ability to cross the blood–brain barrier. They also have no antiemetic, anticholinergic and central nervous system effects unlike the first-generation antihistamines. Drugs like fexofenadine are actively transported into the lumen of the gut, kidney and brain by p-glycoproteins, which restrict their ability to accumulate and cause unwanted side-effects. However, agents such as rifampicin, which induce p-glycoprotein, may increase the clearance of fexofenadine and reduce its efficacy.[45] Second-generation H_1-antihistamines are mostly used as a once-daily dose with minimal risk of developing tolerance. The long-term safety of the second-generation H_1-antihistamines, cetirizine, desloratadine, fexofenadine, levocetirizine, and loratadine, has been documented in randomised controlled trials lasting 6–18 months in adults and in children as young as 1–2 years' old.[46]

Rupatadine fumarate is a newly-launched, second-generation, long-acting histamine antagonist (H_1-receptor antagonist) and platelet-activating factor-receptor inhibitor. Rupatadine fumarate is approved for the treatment of allergic rhinitis and chronic urticaria in adults and children aged 12 years and older. A syrup is available for children aged 2 to 11 years. It inhibits the degranulation of mast cells and the subsequent release of cytokines, more specifically of tissue necrotising factor which is available in mast cells and monocytes.[48]

Ophthalmic (eyedrop) preparations include levocabastine, epinastine, olopatadine and ketotifen (the latter also acts as a mast cell stabiliser). Levocabastine, in addition to azelastine, is also available as a nasal spray for use in patients who suffer from allergic rhinitis.[47]

The leukotriene-receptor antagonists

Examples of leukotriene receptor antagonists include zafirlukast and montelukast. They are competitive antagonists of the cysteinyl leukotriene receptor-1 (*cys*LT-1). They have the advantage of oral administration. Montelukast is also available as a sprinkle

and in a chewable tablet form for convenient use in paediatrics. Montelukast presents an additional option in the management of seasonal allergic rhinitis in children with asthma.[50]

Mast cell stabilisers

They act by stabilising mast cells, thus preventing the release of histamine. The maximum effect is reached after 5–14 days administration, and they are dosed more frequently than topical antihistamines, i.e. four times daily. Therefore, they are not used in the treatment of acute allergic conjunctivitis, and they are reserved for the treatment of SAC in patients that cannot tolerate other therapy.[5]

Conclusion

Allergic conjunctivitis seems to be on a constant rise affecting a large percentage of the population. Allergic conjunctivitis can decrease quality of life and productivity, and the condition can be exacerbated by the presence of comorbid conditions such as rhinitis. The current therapies for the treatment of allergic conjunctivitis, such as antihistamines, mast cell inhibitors and anti-inflammatory drugs are still considered to be effective. The role of the pharmacist is to follow a stepwise approach to treatment. The topical antihistamine/mast cell stabiliser formulations are the first treatment approach because of their ability to relieve symptoms rapidly and they are suitable and well-tolerated for long-term use. However, the development of newer drugs with prolonged duration of action and specificity provides more options. The newly available olopatadine has demonstrated superior effectiveness and is a potential agent of choice in the treatment of SAC or PAC.

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Hypertension – back to basics

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Abstract

This article outlines the principles of blood pressure, including normal and dysfunctional physiology, mathematical equations of pressure, definitions of hypertension and diagnosis, and hence the rationale for and mechanisms of treating hypertension in order to reduce cardiovascular and cerebrovascular risk.

Keywords: hypertension, blood pressure, cardiac output, peripheral vascular resistance

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What is blood pressure?

Blood pressure (BP) is a product of cardiac output (CO) and peripheral vascular resistance (PVR).[1] Hence, changing either or both processes affects BP:

BP = cardiac output (CO) x peripheral vascular resistance (PVR)

CO is mainly associated with systolic blood pressure (SBP), while PVR is mainly associated with diastolic blood pressure (DBP). Breaking this mathematical relationship down further, it is evident that the individual components of CO are related to stroke volume and heart rate:

CO = stroke volume x heart rate

Stroke volume is a function of the three major factors affecting the volume of blood that is pumped out of the left ventricle during each systolic cardiac contraction, namely (i) preload (fluid volume/venous filling), (ii) contractility of the heart, and (iii) afterload (stiffness of the aorta; pressure against which heart has to pump). CO may also increase in many conditions other than hypertension, where the heart rate is increased, e.g. fever, anaemia, exercise, stress, pregnancy, hyperthyroidism, etc., which then presents with elevated SBP in keeping with the formulas outlined above.

Pulse pressure is the difference between SBP and DBP:

Pulse pressure (mmHg) = SBP – DBP

A normal SBP is 120, a normal DBP is 80, and thus a normal pulse pressure is 40 mmHg. Pulse pressure can rise with any clinical condition that has an increased cardiac output, such as fever, anaemia, hyperthyroidism or pregnancy, which causes elevated SBP. This is corrected by treating the underlying cause.

Ageing is associated with stiffening of the aorta and major blood vessels due to loss of elastic tissue. This increases afterload and may cause an isolated systolic hypertension, which is defined as an SBP > 140 mmHg but with a DBP < 90 mmHg. Clearly this would equate to an increased pulse pressure. The concern is that an elevated pulse pressure is associated with an increased mean arterial BP and increased cardiovascular (CV) risk:

Mean arterial BP = DBP + 1/3 of pulse pressure = ± 93 mmHg

What is hypertension?

BP is in a typical normally distributed biological variable curve (Bell shaped) with values at the high end of the distribution curve considered to be elevated BP defined as hypertension.[2]

In a large observational study involving one million adults in 61 prospective trials, there was a proportionate increase in CV risk starting at an SBP level of 115 mmHg and a DBP of 75 mmHg. For every 20 mmHg increase in SBP and 10 mmHg increase in DBP, there is a twofold relative increase in stroke mortality and a two-fold relative increase in mortality from coronary artery disease and other vascular diseases.[3] The absolute CV risk also depends on the presence of other CV risk factors and/or target organ damage as shown, e.g., in the ongoing Framingham Heart Study.[4]

This leads to a very interesting question: What *is* hypertension? (a) Is hypertension a BP level where there is an increase in CV risk? Or (b) Is hypertension a BP level where the benefit of treatment outweighs the harm of the treatment?[2]

Hypertension is currently mostly defined as higher than an arbitrary cut-off level which was chosen for pragmatic reasons to simplify diagnosis and treatment decisions. This arbitrary level of defining hypertension can also be influenced by the absolute or total CV risk of the patient. With a high CV risk, anti-hypertensive drugs may be initiated at lower BP levels.[2,3] BP values defining hypertension could change if and when new information becomes available.

Classification of hypertension

The European Society of Hypertension/European Society of Cardiology criteria to define BP levels are as follows:[5]

- Optimal: SBP < 120 mmHg/DBP < 80 mmHg
- Normal: SBP 120–129 mmHg/DBP 80–89 mmHg

- High normal: SBP 130–159/DBP 85–89 mmHg
- Stage (Grade) 1 Hypertension: SBP ≥ 140–159/DBP 90–99 mmHg
- Stage (Grade) 2 Hypertension: SBP 160–179 mmHg/DBP 100–109 mmHg
- Stage (Grade) 3 Hypertension: SBP ≥ 180 mmHg/DBP ≥ 110 mmHg.

The South African Guidelines follow a similar classification of BP to the European Guidelines. The American guidelines have a different classification and consider a BP of ≥ 130/80 mmHg as hypertension.

How should hypertension be diagnosed?

The basic concept in hypertension diagnosis is that the diagnosis is based on multiple BP measurements taken during many instances and using the mean value of all these readings. Ideally an elevated BP as measured in the clinic (consulting rooms) should be confirmed by an out-of-office measurement such as 24-hour ambulatory monitors or home BP measurements.

Blood pressure measurement methods

Conventional clinic BP (office BP) (This represents a snapshot of total BP load)

In general, this method is less reliable, but the accuracy can be increased by doing repeated measurements at different times of the day and on different days and all the measurements are then used to generate a mean value. At least two BP measurements on at least two occasions using a standard measurement technique, validated equipment, including the correct cuff size, should be the minimum practice.

Measure both arms initially (take highest for the value) and measure BP in one leg to exclude coarctation of the aorta. A marked difference between the two arms indicates the presence of significant atherosclerosis and is associated with an increased CV mortality especially using a cut-off of 15 mmHg.6

Patients with diabetes mellitus, the elderly, especially frail and other people with orthostatic hypotension due to autonomic insufficiency, should have their BP taken 1–3 minutes after standing up. Orthostatic hypotension is defined as a drop in SBP of 15 mmHg or more and a drop of DBP of 10 mmHg or more, especially if accompanied by symptoms such as dizziness.

Unattended automated clinic measurement

In this method, an automated electronic apparatus is used to obtain multiple readings with the patient sitting alone in a quiet room. The automated machine takes 3–5 measurements every five minutes (or at any other time intervals) and the machine then averages all the values. The BP readings taken with this method correlate closely with awake ambulatory readings.6 This method increases the accuracy of the diagnosis of hypertension but must be done properly. The diagnosis of white coat hypertension can also be made with this method.

Out-of-office blood pressure measurements

24 hour ambulatory BP measurements

Advantages of this method are that it is the most accurate method to diagnose hypertension and is therefore considered the gold standard. This method also provides night-time values to demonstrate dipper status which normally occurs when BP falls during sleep. In hypertension, a non-dipper pattern is associated with a worse prognosis. In addition, it provides the total BP load over 24 hours and is useful when episodic hypertension is suspected (e.g. phaeochromocytoma). It can diagnose or confirm white coat hypertension – where the BP is elevated in the clinic but normal outside the clinic – as well as masked hypertension – where the BP is normal in the clinic but elevated outside the clinic.

24 hour ambulatory bp measurements: normal values
Over 24 hours: < 130/80 mmHg
Daytime: < 135/85 mmHg
Night-time: < 120/70 mmHg

Home (self) blood pressure measurements

This method is increasingly used for diagnosis and monitoring BP response to therapy. A normal value is < 135/85 mmHg. It is not possible to obtain nocturnal measurements with this method.

The best and most accurate way to confirm a diagnosis of hypertension is to use at least two different methods.5 True normotension is diagnosed when office BP and one out-of-office measurements are normal.

Hypertension phenotypes based on blood pressure:

1. Dipper pattern: The normal BP pattern is associated with a BP decline at night during sleep. If a hypertensive patient has this BP pattern, it is associated with lower CV risk.
2. Non-dipper pattern: This phenotype does not have a decline of BP at night during sleep and is associated with an increased CV risk. Non-dipper is also associated with obstructive sleep apnoea, obesity, poor sleep quality, high salt intake, chronic kidney disease (CKD), diabetic neuropathy and orthostatic hypotension.
3. White coat pattern: In this phenotype, the BP values taken in the office (clinic) are higher than the BP values obtained outside the office (in ambulatory or home measurements). There could be a slight increase in CV risk in these people and this condition may not be as innocent as previously thought.
4. Masked hypertension pattern (This phenotype is also known as reverse white coat): It has an incidence of 15 to 30% of people with normal BP values in the clinic but elevated BP when tested out-of-office.[7] Exactly how and when to test for masked hypertension remains unclear. It is seen in the elderly but can also be seen in young males with psychological stress. Masked hypertension is associated with a significantly increased CV risk. People with masked hypertension sometimes present with left ventricular hypertrophy of unknown origin with a normal clinic BP measurement.
5. Variable hypertension (especially visit-to-visit): Variable BP readings have been associated with an increased stroke risk.
6. Isolated systolic hypertension (ISH): This phenotype is mainly seen in the elderly with reduced elasticity of arteries: SBP > 140; DBP < 90 mmHg with increased pulse pressure. It carries an increased CV risk and requires treatment.

Causes of hypertension

Essential hypertension (primary or idiopathic) occurs in > 90% of cases. The exact cause of raised BP is unknown, but genetic and environmental factors – high salt intake, decreased potassium intake (as a surrogate for reduced vegetable intake), excessive alcohol intake, smoking, increased calorie intake and sedentary lifestyle all play a role.

Secondary hypertension may be caused by various conditions. These include:

1. Renal disease: CKD is both a cause of hypertension and a consequence of hypertension when damaged as a target organ disease (TOD).
2. Coarctation of the aorta.
3. Endocrine: over secretion of hormones, e.g. Cushing's, Conn's, phaeochromocytoma.
4. Drugs, e.g. nonsteroidal anti-inflammatory drugs (NSAIDs), alcohol, anabolic steroids, cocaine, contraceptives.

Epidemiology of hypertension[5]

Hypertension is diagnosed in 30–45% of adults older than 25 years overall and this high prevalence is consistent across the world, irrespective of income status. The prevalence of hypertension increases with increasing age with a prevalence of more than 60% in people older than 60 years.[5] People aged 80 years have a 90% chance of developing hypertension. Globally, hypertension is increasing, irrespective also of country income status. The major burden of hypertension has shifted to middle- and low-income countries such as sub-Saharan Africa and Asia where most hypertension cases are observed and where the age of hypertension diagnosis has also shifted to younger patients.

Hypertension is the single biggest contributor to CV disease and premature death and is responsible for ± 50% of global myocardial infarctions, stroke, and heart failure and ± 18% of global deaths. Hypertension contributes significantly to renal disease, dementia and to foetal and maternal health. It causes a two-fold increase in risk of coronary heart disease (CHD) and a four-fold increase in risk of stroke and heart failure. Hypertension is responsible for about 35% of atherosclerotic CV events.

Absolute cardiovascular risk in hypertension[3]

In different patients with similar BPs of 145/95 mmHg, the CV risk can vary considerably. The absolute CV risk of hypertension is thus determined by:

1. Level of BP: The higher the BP level, the higher the CV risk.
2. The presence of other CV risk factors: ± 80% of hypertensive people have other CV risk factors.
3. Presence of end-organ damage due to hypertension:
   - Left ventricular hypertrophy (LVH)/heart failure.
   - Proteinuria/renal impairment/renal failure.
   - Abnormal fundus of the eyes such as soft and hard exudates or bleedings.
   - The presence of an atherosclerotic plaque in an artery, e.g. carotid, femoral artery.
   - The presence of existing ischaemic heart disease or stroke or peripheral arterial disease (PAD).

Target organ damage

Complications of hypertension are numerous and include the following organ systems:

1. Heart: LVH – a powerful risk for atherosclerotic complications and heart failure – myocardial infarction (MI), heart failure, arrhythmias (especially atrial fibrillation), aortic valve insufficiency.
2. Aorta: Atherosclerosis, aneurysm and dissection may be caused by hypertension.
3. Peripheral arteries: Atherosclerosis: hyaline arteriosclerosis may occur in small arterioles including in the kidney and retina.
4. Renal: CKD is both a cause of hypertension and a sign of TOD.
5. Brain: Stroke, TIA and possibly dementia.

Severe hypertension[8]

Severely elevated BP causing acute organ damage used to be called malignant hypertension or hypertensive crises. Different levels may cause different injuries. Very high BP (BP > SBP 180/DBP 110–120 mmHg) may cause acute injury to the heart, brain and kidneys, with damage to the microcirculation. Both the absolute level of BP, and the rate at which the pressure rises determine the organ damage.

1. Hypertension urgency: BP severely elevated but there is no TOD.
2. Hypertension emergency: BP severely elevated plus signs of acute TOD. It is reiterated that the speed at which BP rises is important. The basis for the development of complications is endothelium damage by fibrinoid necrosis of blood vessels.
   - Retina: Exudates, haemorrhages, papilloedema.
   - Kidney: Blood in urine (RBC casts) resembles glomerulonephritis picture.
   - Cardiovascular complications are acute MI, acute stroke, and acute heart failure that usually presents with acute pulmonary oedema.
   - Blood: Microangiopathic haemolytic anaemia (RBC fragmented).

Hypertension management principles

The total management of hypertension should include a change in lifestyle as well as drug treatment, with one aim:

To reduce the risk of cardiovascular and renal complications.

The basis of effective management to reduce CVD risk, is to reach target or goal BP and to remain in target or goal BP ranges. This is the concept of target treatment time.[6]

Lifestyle management of hypertension[5]

Healthy lifestyle choices can prevent or delay the onset of hypertension and can reduce CV risks.5 They can also augment the effects of drug therapy and assist in reducing the pill load in some patients. Dietary changes include reducing sugar and refined starch and increasing fruit and vegetables, in concert with increasing moderate intensity exercise to at least 150 minutes per week. Sodium intake should be reduced by not adding salt to food and avoiding salt-rich (preserved) food. Smoking should be stopped, and alcohol consumption and weight should be reduced.

One meta-analysis showed modest reductions in SBP and DBP when lifestyle changes were made.9 This is one of many demonstrating the added benefit of lifestyle changes in lowering BP as an adjunct drug therapy.

Drug treatment of hypertension

Eventually most patients, in addition to lifestyle modification, require drug treatment to control their BP. Licensed anti-hypertensive drugs have been tested in randomised clinical trials and are all associated with reductions in CV events to varying degrees (Table I).

The big question is how to improve BP control in treated patients? The European Hypertension Guidelines5 encourage the use of combination drug therapy in most patients, especially in the context of lower BP targets. Single-pill combination (SPC) therapy of two drugs from different classes, was endorsed by the WHO in July 2019. SPCs improve patient adherence to drug therapy and their use creates a treatment algorithm that is simple, pragmatic and can be applied to all patients regardless of race, gender or age.

When should drug treatment be initiated in hypertension?

The European, NICE (UK) and South African guidelines recommend drug therapy when BP exceeds SBP 140 mmHg and/or DBP 90 mmHg. The big issue is whether treatment should be initiated at a lower baseline BP. When the total CV risk is high (due to other CVD risk factors present or signs of TOD) it could be prudent to initiate drug treatment at a lower level of BP, e.g. SBP > 130 mmHg and DBP > 80 mmHg. This is a controversial issue and is endorsed by the USA guidelines and some others. The bottom line is that people with a high predicted total CV risk should be treated even when the BP does not exceed 140/90 mmHg, such as at BP > 130/90 mmHg.

Treatment schedule for hypertension

The European Society of Hypertension and the International Hypertension Society suggest that treatment is prescribed as follows:

Step 1: Start with a combination of two drugs, preferably in a single pill, of a RAS-blocker (ACE inhibitor or an angiotensin-receptor-blockers [ARB]) and a calcium channel blocker (CCB) such as amlodipine. One can commence therapy with both components at half-dose. If this is inadequate, the dose of both components may be doubled to their maximum recommended doses.

A RAS-blocker plus a diuretic is an alternative combination. The diuretic is useful in the elderly, Black patients, incipient heart failure and CCB intolerance.

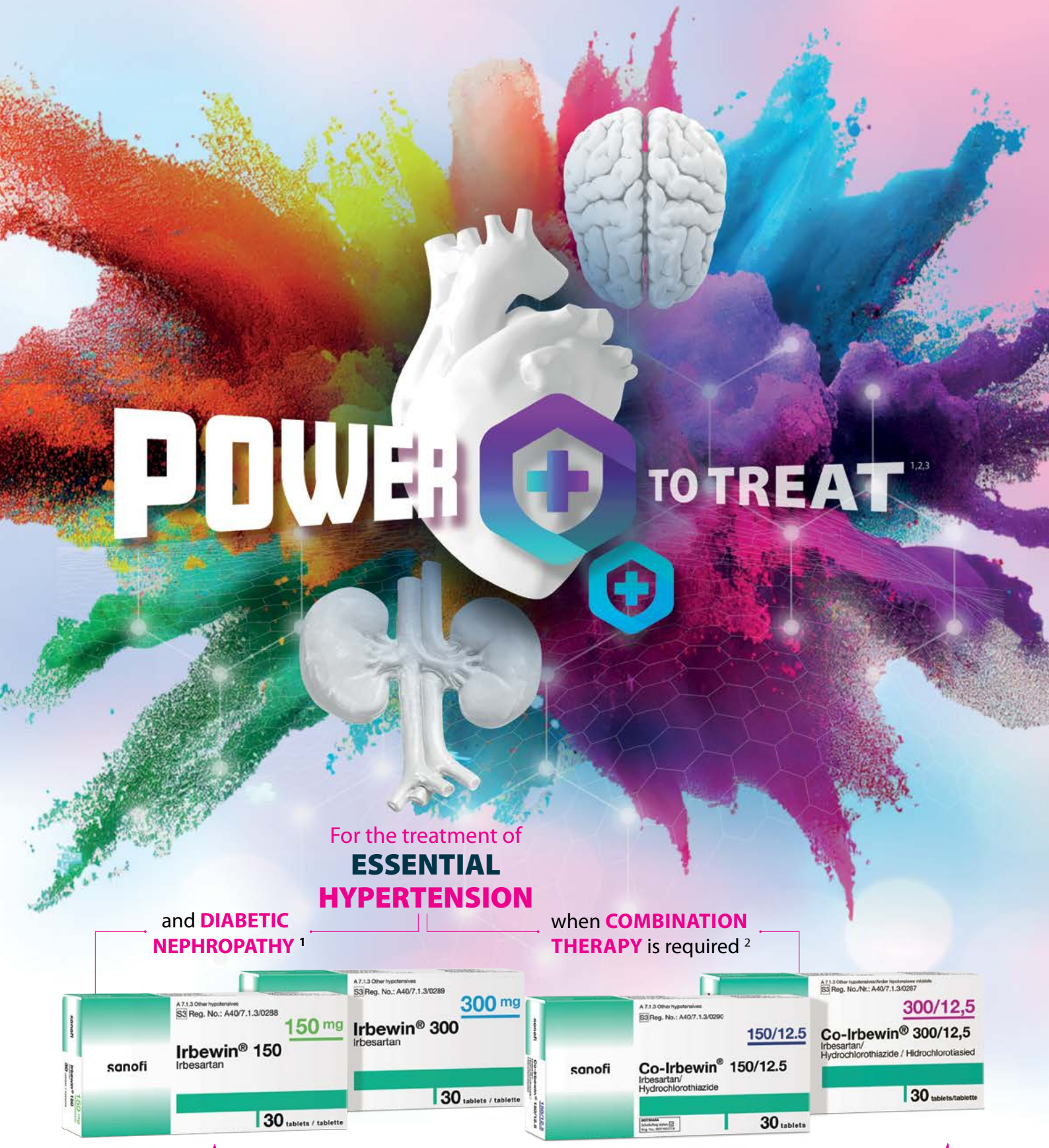
Step 2: If adequate reduction of BP is not achieved, then a triple combination of a RAS-blocker plus a CCB plus a diuretic should be used. Triple drug therapy in a single pill is currently available.

Step 3: Resistant hypertension: BP not adequately controlled despite three drugs, including a diuretic, at full dose. Consider using an aldosterone antagonist (e.g. spironolactone) at doses of 12.5 mg to 25 mg. This agent should not be used if serum potassium is above 5 mmol/l or if there is renal impairment.

Table I: Anti-hypertensive drugs

Class	Types	Examples	Comments
Diuretics	Thiazide-like	Indapamide Chlorthalidone	Available in SA Currently not available in SA
	Thiazide	Hydrochlorothiazide	
	Mineralocorticoid antagonist	Spironolactone; Eplerenone	Aldosterone inhibitors
	Potassium-sparing diuretics	Amiloride	
RAS-blockers	Angiotensin-converting enzyme inhibitors (ACE-I)	Captopril Ramipril	
	Angiotensin-receptor-blockers (ARB)	Candesartan Telmisartan	
Calcium channel blockers	Dihydropyridines (DHP)	Amlodipine; Nifedipine	
	Non-dihydropyridine (NDHP)	Verapamil	
Beta blockers*		Carvedilol;** Bisoprolol;** Metoprolol**	Used 4th line*** or if compelling reasons e.g. MI or heart failure associated with hypertension

*Beta blockers should not be first-line treatment of hypertension except for post-myocardial infarction or heart failure with hypertension
**When heart failure is present, there are only three proven beta blockers that reduce mortality
***Atenolol has been shown not to be as effective in reducing cardiovascular endpoints as the other anti-hypertensive drugs and is especially poor for reduction of stroke



For the treatment of
ESSENTIAL HYPERTENSION
and **DIABETIC NEPHROPATHY** [1]
when **COMBINATION THERAPY** is required [2]

IRBEWIN™
irbesartan

CO-IRBEWIN™
irbesartan/hydrochlorothiazide

References: 1. IRBEWIN 75 mg, 150 mg & 300 mg tablets professional information approved by the medicines regulatory authority. 31 July 2019. **2.** CO-IRBEWIN 150/12,5, 300/12,5 tablets professional information approved by the medicines regulatory authority. 31 July 2019. **3.** Hypertension guideline working group, Seedat YK, Rayner BL, Veriava Y. South African hypertension practice guideline 2014. *Cardiovasc J Afr.* 2014;25(6):288-294.

SCHEDULING STATUS S3 **IRBEWIN® 150/300** (Tablets). **COMPOSITION:** Each tablet contains 150/300 mg of irbesartan respectively. **REGISTRATION NUMBERS:** A40/7.1.3/0288; A40/7.1.3/0289. **SCHEDULING STATUS** S3 **CO-IRBEWIN® 150/12.5; 300/12.5** (Tablets). **COMPOSITION:** Each tablet contains 150/300 mg of irbesartan and 12.5 mg Hydrochlorothiazide respectively. **REGISTRATION NUMBERS:** A40/7.1.3/0290; A40/7.1.3/0288.

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Potential causes of resistant hypertension

1. Measurement issues, e.g. BP measured with an inappropriate cuff size.
2. Treatment issues: Inadequate or non-up titration of anti-hypertensive doses.
3. Doctor inertia to increase drug dose or to initiate combination therapy.
4. Secondary hypertension causes such as hyperaldosteronism, Cushing's and renal disease.
5. Obstructive sleep apnoea.
6. Drugs such as NSAIDS, cocaine, liquorice.

Current recommendation of blood pressure targets (goals) according to European guidelines

Step 1: Aim for a BP of < 140/90 mmHg for all patients, including the elderly.

Step 2: If the patient can tolerate pharmacotherapy without harm (e.g. deteriorating renal function), aim for a BP of SBP < 130 mmHg and DBP below 80 mmHg in patients younger than 65 years. For patients older than 65 years, a goal of < 140/90 mmHg should be adequate. (Be careful with immobile frail elderly patients.) There are some indications that a lower target for the elderly may be beneficial. Measure BP in the elderly in the standing position because of the high prevalence of orthostatic hypotension in this age group.

If using home and ambulatory BP measurements, aim for BP of < 135/85 mmHg.

The important issue is to not only aim for the target BP, but to keep the BP at target at all times.

Effect of treatment

The Thomopoulos et al. meta-analysis[10] of 68 randomised clinical trials involving 245 885 patients who received anti-hypertensive drugs has shown the following results for a reduction of SBP of 10 mmHg and DBP of 5 mmHg over five years of treatment:

Relative risk reduction of stroke: 36% (95% CI 29–43%) with numbers-needed-to-treat (NNT) of 53 (95% CI 45–65) to prevent the first stroke over five years.

Relative risk reduction of coronary heart disease (CHD): 18% (95% CI 14–24%) with NNT of 133 (95% CI 100–171) to prevent the first CHD event over five years.

Relative risk reduction heart failure: 38% (95% CI 25–49%) with NNT of 53 (95% CI 42–79) to prevent the first heart failure over five years.

Relative risk reduction of CV death: 16% (95% CI 8–23%) with NNT 125 (95% CI 88–249) to prevent the first CV death over five years.

The relative risk reductions are very similar for hypertensive patients with and without diabetes mellitus. The absolute risk reductions are higher and better with higher CV risk patients.

A rather contentious issue is to what level should the DBP be reduced before possible ischaemic damage to the myocardium occurs? The conventional target DBP should probably not be lower than 60 mmHg. There is, however, insufficient trial data to be absolutely sure.

Conclusion

The following may serve as a framework for the management of a patient with hypertension:

1. Diagnosis of hypertension: multiple readings are necessary using clinic or 24-hour ambulatory or home measurements. The clinic (office) BP measurement is regarded as screening for hypertension and an out-of-office measurement is necessary for confirmation of diagnosis.
2. Look for obvious secondary causes: Sometimes the phenotype of the patient will aid the diagnosis, e.g. the Cushing's-phenotype.
3. Test for other CV risk factors: More than 80% of hypertension patients have other CV risk factors. Treat these if present alongside BP treatment, e.g. the use of statins in hypertension is associated with additional reductions in MI.
4. Test for TOD using a resting ECG for LVH and urine dipstick for the presence of proteinuria. These are the minimum tests.
5. Regarding treatment, start with lifestyle changes which may aid in the treatment and contribute to BP reduction. Eventually patients will need drug therapy. Lifestyle changes may also enable one to reduce the pill load. Typical measures which can be taken are the reduction of salt intake, cessation of smoking, exercise, reduction of alcohol intake and increased vegetable and fruit intake.
6. Achieve goal BP levels and maintain BP below target or goal levels. Review the progress of the patient regularly. Control of BP is essential and preferably must be achieved within at least the first three months to maximise the benefits of treatment.

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What to expect when being inspected – An overview of the processes involved in the inspecting of community pharmacies

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Introduction

Pharmacy council inspectors play a crucial role in ensuring the quality, safety, and compliance of pharmacies with established regulations and standards. These inspectors are typically appointed by pharmacy regulatory bodies in South Africa, the South African Pharmacy Council (SAPC). It is important for both the responsible pharmacists and other pharmacists to be aware of the functions of these inspectors and what would be expected of them. Pharmacists have the right to expect that any sensitive patient information or confidential business information observed or discussed during the inspection will be kept confidential. It is important for pharmacists to be informed of any specific standards or requirements being assessed during the inspection. After the inspection, pharmacists have the right to receive a written report (provided in a timely manner) that details the findings of the inspection, including any deficiencies or areas of non-compliance. In many cases, pharmacists have the opportunity to correct any deficiencies or violations identified during the inspection. If pharmacists disagree with the findings or actions taken by the regulatory council as a result of the inspection, they may have the right to appeal the decision. Pharmacists should conduct themselves professionally and cooperatively during the inspection process. Additionally, open communication and cooperation with the SAPC can help ensure a smooth and productive inspection process. If pharmacists have concerns or questions about an inspection, they should consider seeking guidance from the SAPC or their professional organisation.

The pharmacy council inspector needs to regularly visit and inspect pharmacies, to make sure that:

1. **Patient safety and quality assurance:** Inspections help to ensure that pharmacies are providing safe and effective medications to patients. By evaluating the storage conditions, dispensing practices, and overall quality of medicines, inspectors help prevent errors that could harm patients.
2. **Compliance with regulations:** Regulations are put in place to safeguard public health. Inspectors ensure that pharmacies adhere to these regulations, which include requirements for the storage, handling, dispensing, and labelling of medications. This ensures that pharmacies are operating within the legal framework and maintaining ethical practices.
3. **Preventing counterfeit medicines:** Inspectors can verify the authenticity of medications and track their sources, which is essential in preventing the distribution of counterfeit drugs. Counterfeit medicines can pose serious risks to patients' health.
4. **Controlled substances and drug abuse prevention:** Inspections help to monitor the proper handling and dispensing of controlled substances, such as opioids and other potent medications. This oversight is critical in preventing drug abuse, diversion, and illicit distribution.
5. **Pharmacist competence:** Inspectors assess the qualifications and competence of pharmacists and pharmacist's assistants. Ensuring that staff are adequately trained and knowledgeable contributes to the safe and effective delivery of pharmaceutical care.
6. **Proper documentation:** Inspections verify that pharmacies maintain accurate records of prescription orders, dispensing activities, and patient interactions. Proper documentation is essential for tracking patient history, ensuring accountability, and addressing any potential issues that arise.
7. **Facility conditions:** Inspectors evaluate the physical infrastructure of the pharmacy to ensure that it meets standards for cleanliness, organisation, and appropriate storage conditions. This helps prevent contamination and degradation of medications.
8. **Adverse event reporting:** Inspections contribute to pharmacovigilance efforts by identifying adverse events or incidents related to medications. This information can be used to take appropriate measures to prevent similar incidents in the future.
9. **Continual improvement:** Inspectors provide feedback and recommendations for improvement to pharmacy owners

and managers. This encourages pharmacies to continuously enhance their practices and maintain a high standard of care.

10. **Public trust:** Regular inspections enhance public trust in the healthcare system by demonstrating that pharmacies are being held accountable for their practices. When patients have confidence in the safety and quality of their medications, they are more likely to adhere to prescribed treatments.

The Pharmacy Act, No.53 of 1974, directs our statutory body, the South African Pharmacy Council (SAPC), to perform inspections of our premises in order to uphold and regulate the laws of the industry.

Monitoring, training, and disciplinary inspections in all categories of pharmacies (new and existing) are conducted by inspection officers. These officers, whose identities are disclosed on the Council website in the Inspection Officers Catalogue (available from https://www.pharmcouncil.co.za/Media/Default/Documents/Inspectors%20Catalogue%2022-1.pdf), are tasked to assist Council in the maintenance and control of standards of pharmacy practice in both the public and the private sector. These inspections can be classified as follows:

- Training facility inspection
- Monitoring or routine inspection
- New premises inspection
- Follow-up inspection
- Disciplinary inspections

In order to become an inspection officer, the individual must be a registered pharmacist in good standing with Council and who honours the policies and objectives of Council and abides thereby in the execution of his or her tasks. The Council trains the appointed inspection officers during an annual Lekgotla and several ad-hoc meetings to strive towards a uniform standard of inspection practice.

Appointments are scheduled for inspections regarding Training Facility or New Premises applications, but all other inspections could be unannounced visits.

There are two types of Council inspection officers:

- Routine
- Disciplinary

However, some inspectors can be tasked to undertake both roles.

Community pharmacies can also be inspected by the South African Health Products Regulatory Authority (SAHPRA). SAHPRA have their own inspectorate and may be accompanied by the South African Police Services (SAPS) during certain visits. These types of inspection are not routine and could include search and seizure warrants.

A pharmacist may NOT prevent an inspection officer from Council or SAHPRA from entering the pharmacy and conducting an inspection. Any person who fails to give or refuses access to inspection officers appointed by Council when they request entrance to any pharmacy, who obstructs or hinders them in the execution of their duties under the Act, who fails or refuses to give information that they may lawfully be required to give to such an officer, or who gives false or misleading information to such an officer knowing it to be false or misleading will be investigated in terms of Chapter 5 of the Act.

It is important that all professionals understand the intention and mandate of inspection officers as they should serve the public and the pharmacy profession in an unbiased and impartial manner in order to create confidence in the Council and the profession. It is expected that inspection officers should treat members of the profession and the public as customers who are entitled to receive a high standard of service and may not discriminate unfairly against any member of the profession or the public on whatever basis.

Role of Council

The role of the inspection officers is to assist Council in achieving two of its primary objects in terms of the Pharmacy Act 53 of 1974:

- to uphold and safeguard the rights of the general public to universally acceptable standards of pharmacy practice in both the private and public sector
- to establish, develop, maintain and control universally acceptable standards of practice of the various categories of persons required to be registered.

The inspection officers are responsible for conducting inspections at manufacturing, wholesale, community, and institutional pharmacies in order to assist in the maintenance and control of standards of pharmacy practice in both the public and the private sector.

Council utilises the services and expertise of 37 inspection officers. Pharmacists should note that the inspection officers are not obligated to make an appointment and that they can arrive unannounced at any time. To be ready for an inspection, ensure that you comply with the rules pertaining to good pharmacy practice (GPP) and other applicable legislation. Complete the Self-Inspection Questionnaire for the relevant category of pharmacy. These are available online via the Council website.

All inspection officers must at all times behave in a way that upholds the Council's values, integrity, and good reputation. They are obliged to advise the Council as soon as possible as they become aware of any actual or possible conflict of interest, financial or otherwise. Examples of this include that an inspection officer may not inspect his/her own pharmacy, or that of a family member or close friend, nor pharmacies where they have a financial benefit (shareholding) or that of a competitor (if they own a pharmacy).

Powers of Council to achieve its mandate

- To inspect the records and accounts of or investigate the activities at a pharmacy carried on by a person so registered.

These powers are delegated to inspection officers appointed by Council.

- Powers of inspection officers:
  - An inspection officer may enter any pharmacy at any time reasonable in order to conduct an inspection as requested by Council.
  - They will have a document confirming their appointment as a Council Inspection Officer signed by the Registrar of Council. This is renewed on an annual basis.
  - This document must be shown to the pharmacist on entering the pharmacy.
- Any person who refuses access, obstructs, hinders, fails to supply requested information, or furnishes false information to an inspector, is guilty of an offence
- The Council may obtain a warrant authorising an inspection officer, alone or with assistance from the SAPS, to close a pharmacy for not more than 90 days pending an investigation into possible contraventions of the Medicines Act deemed to be a risk to public health.
- Inspection officers have the obligation to report to Council any act which constitutes an offence, or which is prejudicial to the public's, the Council's, or the profession's, interest.

In the performance of their duties, an inspection officer should always strive to achieve the objectives of Council in a cost-effective manner and in the public's interest. Officers should be punctual and should execute their duties in a professional and competent manner. Although inspection officers should always promote sound, efficient, effective, transparent, and accountable administration, they are under no obligation to inform pharmacies of the intended inspection, prior to such inspection, and may arrive unannounced. Ultimately, inspection officers should be committed to the development and upliftment of the profession, respecting, and protecting every person's dignity and his or her right as contained in the Constitution of the Republic of South Africa. Under no circumstances should an inspection officer ever use their official position to obtain private gifts or benefits for themselves during the performance of his or her official duties nor does he or she accept any gifts or benefits when offered as these may be construed as bribes. Similarly, inspection officers should also not abuse their position to promote or prejudice the interest of any member of the profession.

In turn, pharmacists should treat the inspection officer with respect and in a cooperative manner. If at any time a pharmacist feels that an inspection officer has violated the code of conduct, then the pharmacist has the right to lay a complaint against the inspection officer with the Council.

Routine inspections

After conducting a routine inspection, a pharmacy would be graded as follows:

- Grade A Pharmacy: minor shortcomings identified; cycle for inspection three years
- Grade B Pharmacy: major shortcomings identified; cycle for inspection two years
- Grade C Pharmacy: critical shortcomings identified; cycle for inspection one year

The costs of a routine inspection of Grade A and Grade B Pharmacies are included in the pharmacy annual fee. Grade C pharmacy inspections attract an inspection fee each time the pharmacy is inspected.

Please note that the inspection report, shortcomings document and Grading Certificate will be available on the Council website for the Responsible Pharmacist [RP] to access after the inspection. The process and timelines for the inspection report are managed by Council and the inspectors are not involved post the submission of the report. Ask the inspector to assist you to access the website and show you where to find the reports before he/she leaves. The RP must reply to Council within 21 days of receiving the Shortcomings Letter with a written response or explanation. Grading certificates will also be posted to the pharmacy and the original must be displayed in the pharmacy.

Rights of the pharmacists when being inspected

Pharmacists in South Africa, like in many other countries, have rights and responsibilities when they undergo inspections by regulatory authorities (e.g. Council or SAPHRA). These inspections are typically conducted to ensure that pharmacists and pharmacy practices comply with the above-mentioned laws, regulations, and professional standards. Embedded in this article is a hyperlink to a SOP, to provide guidance to pharmacy owners and Responsible Pharmacists (RP)s on the self-inspection, pharmacy inspection processes and preparations ahead of an inspection. Here are some general rights and considerations for pharmacists during inspections:

- Fair treatment with no favour or abuse.
- Polite and helpful dealings with the inspection officer who undertakes a coaching role.
- Entitled to receive a high standard of service. The inspection officer is an ambassador of Council.
- No discrimination with respect to race, gender, ethnic or social origin, colour, sexual orientation, age, disability, religion, political persuasion, belief, culture or language.
- Right of access to information. The pharmacist has a right to read through the inspection report, has a right to comment on the report; if they do not agree with any comment they may state so in the report. Pharmacists have a right to a copy of the inspection report.
- The inspection officer does not have to schedule or give notice of an intention to perform an inspection except for new premises and training facility inspections.
- Confidentiality.

- The inspection should not interfere with the normal running of the pharmacy and the pharmacist can ask the inspection officer to wait while patients are attended to.

Conclusion

Council inspection officers are legislated to ensure that pharmacists are upholding the regulatory requirements, maintaining professionalism, and most importantly providing health care that is of the highest standards. To ensure that the pharmacy profession maintains high standards, establishing a good rapport between pharmacist and inspection officer remains key. Pharmacy Council inspectors play a vital role in safeguarding patient health, ensuring regulatory compliance, preventing drug-related problems, and maintaining the overall integrity of the pharmaceutical industry. Their work contributes to a safer and more reliable healthcare system.

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Therapeutic patient education in atopic dermatitis

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Abstract

The successful management of chronic diseases such as atopic dermatitis relies greatly on adherence to treatment. The likelihood of adherence requires much more than a simple transfer of knowledge: a change in individuals' behaviour towards health is needed. One of the critical components of this change is therapeutic patient education. This form of education is an evolving concept: it aims to empower patients and their caregivers with the knowledge and skills to be able to manage disease autonomously. Despite the obvious challenges, this Darwinist approach to healthcare should be embraced in medicine, and in particular in the care of atopic dermatitis patients, in order to ensure an improvement in patients' (and their caregivers') quality of life.

Keywords: atopic dermatitis, eczema, self-management, education, adherence

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Introduction

Never has it been clearer than during the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic that atopic dermatitis (AD) sufferers needed to be empowered to manage their own skin conditions. On 27 March 2020 the start of a strict lockdown was announced in South Africa to curb the spread of the novel corona virus. Suddenly, a specialist dermatology clinic that usually saw 20–30 AD patients per week saw only a handful of emergency cases. This de-escalation of services continued for many months and specialist healthcare involvement in patients' care was severely disrupted. AD patients were literally left to their own devices.

This review focuses on the evolving concept of therapeutic patient education (TPE) and how it can be harnessed to empower AD patients and their caregivers.

What is therapeutic patient education?

In the 1970s, Jean-Philippe Assal, a Swiss endocrinologist, became aware that more than half of patients affected by chronic diseases did not follow the treatment plan suggested by their doctor. He acknowledged that those diagnosed with a chronic disease (which is by definition incurable) experienced a temporary disruption in their lives and an emotional shock following the realisation that they would have to live with the condition for the rest of their life. Healthcare practitioner (HCP) training is focused mainly on caring for acute illnesses. But if fewer than 10% of conditions are acute and more than 80% of cases are of a chronic nature, that creates a huge discrepancy.[1]

In 1998, the World Health Organisation (WHO) published a document outlining an educational programme for HCPs 'in the field of prevention of chronic diseases and therapeutic patient education' after identifying a lack of knowledge in that regard.[2]

The programme was developed initially for conditions such as diabetes mellitus (DM), cardiovascular disease and asthma, but it has now been extended to include other chronic conditions, including AD and psoriasis. The aim is to help patients gain the skills required to manage their chronic diseases and to improve their everyday lives.

TPE is not simply the transfer of information.[3] Merely providing information – for example, through leaflets in a waiting room or a didactic-type lecture – is not adequate to lead to the long-term goal of self-management of a disease. The archaic patriarchal physician-centred model where the doctor knows more than the patient and the doctor decides what treatment plan the patient follows works well in acute situations. But with chronic diseases knowledge is not always the problem. Patients often have the information, but for this information to lead to health-behaviour change more is needed. For example: most smokers know that cigarette-smoking is harmful to their health and want to quit. But despite the knowledge of the health risks, most do not quit. This is where the newer patient-centred physician–patient relationships become important. The precise ingredients of effective interventions remain unclear, but they are likely to require the following:

- motivation on the part of the patient;
- shared decision-making (patient-centredness);
- the development of problem-solving skills;
- realistic goal-setting; and
- agreement on action plans.

This all needs to be combined with adequate knowledge and skills and should lead ultimately to the patient developing the confidence to self-manage their condition.[4]

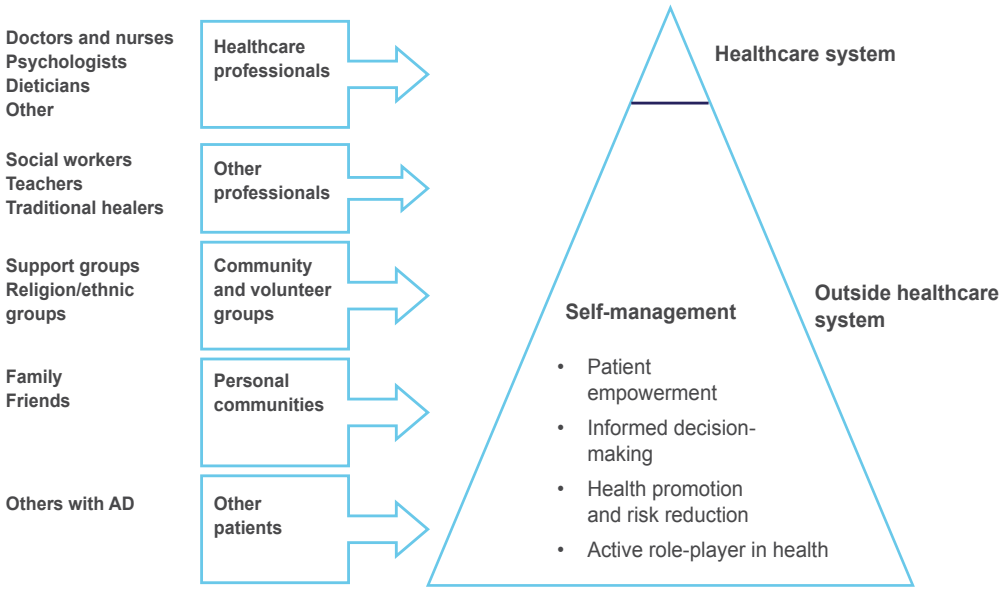

Figure 1: Self-management of AD and other chronic diseases

Why is therapeutic patient education important?

As we know very well, AD is a chronically relapsing inflammatory skin condition, one that is characterised by severe pruritus. Not only can the effects of pruritus be compared to those of chronic pain, but the chronically systemic inflammation is also now known to have much more far-reaching consequences – among other factors, mental-health diseases and cardiovascular complications.[5,6] AD may also predispose to a higher risk of other atopic disorders, often referred to as the 'allergic march'.[6] The effect on quality of life (QoL) of patients and their loved ones has been published – especially in recent years.[7,8] At a psychological or an emotional level the impact can be enormous.

During early childhood, the major impact will be on caregivers – the silent sufferers. Feelings of helplessness in their inability to reduce their child's suffering, frustration with the medical fraternity, guilt, exhaustion and financial pressures prevail.[8] The older child will often have poor and interrupted sleep and could display hyperactivity, irritability and disciplinary problems as a consequence, which will affect the trajectory of their lives negatively. Restricted outdoor play, restricted clothing, bullying and avoidance by other children and adults due to the visible nature of the disease make them aware of the fact that they are different – something that most children and early teens do not want to be.[9]

During their adolescent years, AD sufferers are more likely to experience psychological problems than their healthy peers. Suicidal ideation may be a particular problem in late adolescents. The social isolation experienced in childhood affects their self-image and body image, which leads to problems with intimacy and personal relationships.[10] In adulthood, additional stressors such as financial concerns and those regarding absenteeism from work, relationship pressures and the fear that their offspring may inherit the disease from them are added on.[11]

The financial burden of the disease is difficult to comprehend because there are many direct and indirect costs (such as absenteeism and presenteeism) which are impossible to place a monetary value on. Direct medical costs depend on different countries' healthcare services. Information about this can be found in articles by Laughter et al and Chung et al.[12,13] South African data are currently being prepared for publication.

Skin diseases affect almost one-third of the world's population and are the fourth most common cause of all human diseases. The burden is often underestimated, though. The burden of disease is determined by the disability-adjusted life-year (DALY), which is 'calculated as the sum of the years lost due to specific premature mortality and the years lost due to disability'.[14] In a publication reporting on the results of the Global Burden of Disease Study AD ranks 15th of all non-fatal diseases and top among skin diseases.[12]

Owing to the chronicity of AD and the constant pressure on the healthcare service, the emphasis in managing this condition needs to be mainly on the patients themselves, their caregivers and the global village at large. The very small role that the healthcare system plays and the importance of self-management are strikingly demonstrated in Figure 1.[15]

The successful management of the disease requires a patient to adhere to their treatment. Until 2003, the term 'compliance' was preferred to describe patient adherence to the prescribed management suggested by their doctor. This reflected the more paternalistic physician-centred model and tended to lead to negative emotions. After 2003, with the adoption of the deliberative patient-centred model, the preferred terminology changed to 'adherence'. This implies that the doctor and the patient have equal roles to play in the management of the chronic disease.

The most common cause of treatment failure is poor adherence. Distinguishing between non-adherence and non-response is critically important because the latter has therapeutic implications for the patient that may be unnecessary and may even be detrimental to the patient's health and finances. It is therefore paramount to employ adherence-improving strategies to optimise the chances of patient adherence.

What does the evidence say about therapeutic patient education?

Numerous studies have proven the efficacy of TPE in managing chronic diseases, including DM, asthma and rheumatoid arthritis.[16–18] Not only has it been proven to increase the knowledge but also – and most importantly – the QoL of these individuals. These have proven so successful that official recommendations have been published for asthma and DM.[19] In a publication by Lagger et al, 35 meta-analyses from 1999 to 2009 were analysed critically.[20] The conclusion was that 64% of studies found improved patient outcomes – across all diseases. The impact of TPE on health outcomes was found to be 50–80%.[20]

Does therapeutic patient education work for atopic dermatitis, though?

In the most recent Cochrane database review on the subject, ten randomised control trials (RCTs) could be included. Despite the heterogeneity of the designs and the non-standardised outcomes, the authors concluded that the process 'showed promise'.[21] The inclusion of paediatric studies in particular, involving multidisciplinary teams or nurse-led clinics, seemed to reduce disease severity and improve QoL.[21] In contrast, those interventions where the educational component was less than 30 minutes or where lay people were involved were found to be less effective. Those led by dermatology nurses were more effective compared to the doctor-led programmes.[22] In 2017, a prospective randomised controlled multicentre study evaluating the efficacy of the well-established ARNE programme from Germany ('Arbeitsgemeinschaft Neurodermitisschulung fur Erwachsene') was conducted on an adult AD group. This 12-hour programme involved age-appropriate group sessions led by a multidisciplinary team comprising a dermatologist, an allergologist or a paediatrician, a dermatology nurse, a dietician and a psychologist. At one year of follow-up, the intervention group (n = 168) showed a significant improvement in coping with itch ($p < 0.001$), QoL ($p < 0.001$) and the severity of disease ($p < 0.001$) compared to the control group (n = 147).[23] An International Eczema Council position statement published in 2021 confirmed the importance of structured TPE programmes to managing all age groups with AD.[22] The prominent role of TPE is reiterated when we look at the very first entry in the base of the AD treatment pyramid recommendations published in 2020 by the European Task Force on Atopic Dermatitis/European Academy of Dermatology and Venerology (ETFAD/EADV) for all age groups and across all severities.[24]

Table I: Guide to educational visit

- Ask about the history of the disease.
- What do you think is the cause of the disease?
- Is there anything that worsens or improves the condition?
- What bothers you the most about the disease?
- How are you treating the disease?
- Describe your treatment in detail, please?
- Do you think the treatment is working?
- Are you worried about any of the treatments?
- Are you limited in any of your daily activities?
- How are you experiencing relationships with family, friends and work colleagues?
- What do you do or whom do you ask if you see that you

Who can potentially benefit from therapeutic patient education in atopic dermatitis?

TPE should always be offered to patients – although it remains their decision whether they would like to participate or not (the patient-centred approach). At face value, all those involved will stand to benefit from effective TPE, but that may not always be realistically possible. Those who stand to gain the most are moderate–severe AD patients, especially those who have displayed a failure of therapy. TPE should also be offered to those who seem to struggle with adherence, suffer from corticophobia and have poor social support.[25] During early childhood, TPE is aimed at the caregivers; and as the child ages, the focus of TPE is transferred to the child themself. Practically, for those patients under the age of eight years, the main focus will be the caregiver: for those between eight and 12 years of age, the patient and the caregiver should be included. In patients over the age of 12 years, the patient would be the main focus. These ages are empirical and are as suggested by the ETFAD/EADV Eczema Taskforce.[24]

Therapeutic patient education: the four-step process

Before starting the four-step process, introduce the patient to the concept of TPE. Explain the goals and benefits and what the specifics of the sessions would be: for example, the timing and the venue. If the patient decides to proceed, establish the patient's consent. Then the actual four-step process can commence.[25,26]

The initial step is to ascertain the patient and/or the caregiver's knowledge, beliefs and expectations. After that, age-appropriate educational goals should be set. Then follows the transfer of knowledge and skills. Finally, the efficacy of the process should be evaluated. These steps are depicted in Figure 2.

Step 1: Educational diagnosis

This should be an individual visit (ie not in a group format) and can be doctor- or nurse-led. The duration can be 15–60 minutes or longer. The main educational points to focus on will be the severity of the disease, how it affects their daily lives, how they are managing the disease and whether they are experiencing any barriers in their adherence to the treatment. These may include corticophobia (raise this very carefully and non-judgementally),

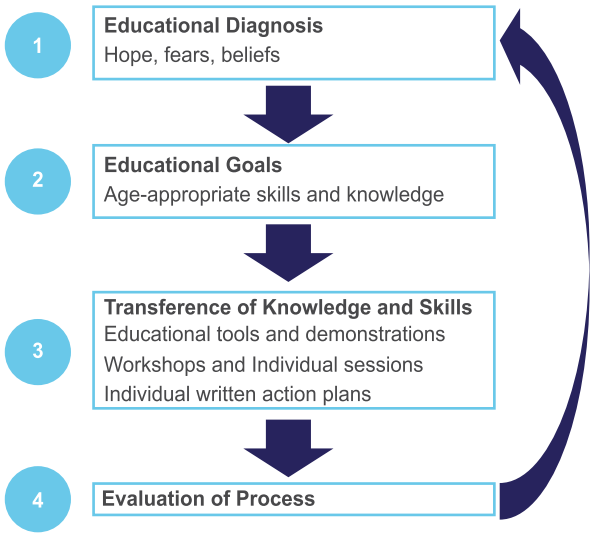

Figure 2: Therapeutic patient education: The four-strep process

time limitations, complexity and/or costliness of the treatments. A guide to some of the questions that can be raised during this visit is provided in Table I.

Step 2: Educational goals

This is the 'skills to be acquired' phase. These goals need to be delineated in collaboration with the patient and/or the caregiver. The goals should be age-specific and particular to the patient's unique situation. This may be a good time to discuss the basics of the disease – in particular its chronicity – if this has been identified as a gap in the knowledge in Step 1. If the patient or the caregiver does not realise the long-term implications of the disease, they may not grasp the necessity of acquiring the specific skills. The goals can be categorised broadly into knowledge about the disease, the practical skills required and the relational skills required. A practical way of doing this would be to ask what they think they would need to know to be able to cope with the various challenges of the disease – mention these by name. Examples of these statements can be found in Table II. With these goals having been expressed, a personalised programme can be developed for each patient.

Step 3: Transfer of knowledge and skills

Various educational resources can be used to transfer the necessary knowledge and skills. A personal written action plan is of critical importance to increase adherence. Much of the information shared may be new and may be overwhelming and therefore it will need to be digested following the discussion.[27,28] A free downloadable action plan for children is available on the Allergy Foundation of South Africa's website (www.allergyfoundation.co.za). Educational resources such as printed leaflets or booklets, multimedia such as short films, and online or in-person interactions are options. More individual sessions may be required or collective therapeutic education sessions such as lectures or workshops may be used. Each of these has advantages and disadvantages attached to them. For example, workshops are more personal but lectures may be able to reach more people. Peer-to-peer interactions would certainly enrich these encounters.

Table II: Examples of educational goals

I would like to know
- what to do when I itch/when my child itches.
- how to adapt my treatment when my skin gets better and when it gets worse.
- how to apply the creams.
- how to do a bleach bath.
- how to use my medication.
- how to be able to recognise a flare.
- how to recognise a complication (eg infection).
- when to ask for help and who to contact.
- how to explain AD to my friends/to my partner/my work/the school.

In an ideal world these sessions should be led by a team of 2–3 people, including doctors (dermatologists, allergologists and/or paediatricians), dermatology nurses, psychologists and dieticians. What is feasible and cost-effective in a particular setting should be determined in a manner that focuses on the AD patient.

Step 4: Evaluating the efficacy of the four-step process

The three main elements included in the evaluation should be the patient, the programme and the economic impact. Examples of assessments and their timings are given in Table III. Establishing whether educational goals were met should preferably be evaluated during a follow-up appointment. This could be with the medical practitioner or a speciality nurse. In the interim, simple questionnaires can explore whether the information was assimilated. Uncertainties and gaps in knowledge can be raised during the follow-up appointment.

What is important to keep in mind is that this four-step process should not be the end of the educational road. The course of AD is fluid and as problems are identified those can be dealt with by the similar four-step process. HPCs will therefore keep evaluating and re-evaluating for the benefit of the patient.

Practical considerations

Around the world, many hospital teams have developed 'eczema centres' or 'atopic schools'. These programmes differ in their content, processes and organisation.[29] Examples include the formalised ARNE programme in Germany, on the one hand, and the much more informal Brazilian patient-support groups, on the other. Even in the Brazilian programme attendants demonstrated a 75% improvement in AD after having attended a meeting.[22] There is no one correct way. Programmes need to be individualised by country, by region, by cultural and language differences, to mention only a few.

South Africa is a very diverse country with many healthcare and financial limitations. Language and cultural differences are much more problematic than one may think, as was demonstrated by Levin in 2006.[30] Simply translating words may not be enough, because certain words commonly used by HCPs may not exist in a patient's vocabulary or may have a completely different meaning.

Table III: Evaluating the efficacy of the TPE-process[25]	
Assesssment	**Timing**
The patient:	
• Severity scores (SCORAD/EASI)	Before and after process, six months, 12 months
• Self-assessment scores (PO-SCORAD)	Monthly
• QoL scores (DLQI)	Before and after process, six months, 12 months
• Simple questionnaire – knowledge	Before and after process
The programme:	
• Patient and parent satisfaction questionnaire	Before and after each session
Economic impact:	
• Number of days hospitalised, work productivity, treatment costs	Six months, 12 months

Culture-specific models of disease dictate the understanding of causality of disease and therefore has a huge influence on successful treatment. If the HCP is not aware of this, their communication will be discordant.

Possessing local knowledge of cultural beliefs and harnessing the use of translators with a basic knowledge of a disease will be critical to success in educational interventions. Additional barriers may be crime rates and, of course, patients' inclination to decline intervention.

Conclusion

While we are in the dawn of a bright new era for AD, with new medication being developed daily for a more personalised approach, the efficacy of the management remains dependent on adherence to treatment. An effective and targeted multidisciplinary TPE programme that is patient-centred will equip patients with the knowledge and skills (physical and emotional) to cope with the challenges of the disease and to improve their lives.

(Please refer patients to the AD Support Group on Facebook/Meta: http://www.facebook.com/groups/saeczemasupport/)

Conflict of interest

The author declare no conflict of interest.

This article has been peer reviewed.

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Allergic rhinitis in children: Comparing South African recommendations and European guidelines

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Abstract

Allergic rhinitis (AR) is a common condition that affects children from a very young age. It is often misdiagnosed as viral rhinosinusitis and erroneously treated with first-line over-the-counter medication, which will not only be ineffective, but may also lead to medication side-effects. Untreated AR can lead to serious complications. Trigger identification can be done using skin-prick testing and serum IgE-measurement – but this should be performed early. However, in certain emerging AR phenotypes – for example, local allergic rhinitis (LAR) – these procedures may have negative results and a nasal allergen challenge should be performed. This review aims to highlight some basic principles of diagnosing, investigating and treating AR in South African children and to compare existing South African guidelines with recently published European guidelines. Early aeroallergen immunotherapy has a disease-altering effect on the natural course of AR, but access to this treatment option is unfortunately too expensive for most patients in South Africa. It is time for health authorities and stakeholders to realise that immunotherapy is more cost-effective than pharmacotherapy in treating this debilitating chronic disease which often seriously interferes with a patient's quality of life.

Keywords: rhinitis, allergy, immunotherapy, EUFORIA, SAARWG

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Introduction

Clinically, chronic rhinitis is divided into infective and non-infective rhinitis. Allergic rhinitis (AR), a phenotypical sub-group of non-infective rhinitis, is a disease complex that is characterised by two or more symptoms of rhinorrhoea, sneezing, itching and nasal blockage.

The prevalence of AR in South Africa varies. The International Study of Asthma and Allergies in Childhood (ISAAC) – a questionnaire-based cross-sectional study – has clearly indicated an increase in AR prevalence over time. For instance, during ISAAC phase I (1995) the prevalence of self-reported AR symptoms during the preceding 12 months in 13- to 14-year-old children from Cape Town, South Africa, was 30.4%. In ISAAC phase II (2002) the prevalence increased to 38.5%.[1] By using protocols similar to ISAAC phase I, a prevalence study done during 2012 in children 13 to 14 years of age was conducted in Ekurhuleni, Gauteng province. The prevalence of self-reported rhinitis was 52% (rhinitis – ever) and 40% (rhinitis – current). For rhinoconjunctivitis and hay fever, the prevalence was reported as 21% and 37% respectively. The importance of environmental exposure to truck-traffic emissions was highlighted as an important driver of these symptoms.[2]

In young children, the prevalence of AR is unknown. Although AR symptoms can present in children from as young as two years of age – often misdiagnosed as recurrent viral upper respiratory infections (URIs) – the prevalence is higher in older children and adolescents. Some authors report an increase in AR prevalence of approximately 2% per year of age.[3]

Diagnosis and complications of allergic rhinitis in children

The differential diagnosis of chronic rhinitis is broad. It is therefore essential to take a thorough clinical history and perform a meticulous physical examination on a child with suspected AR. Itching eyes and an itchy nose (rhinoconjunctivitis), rhinorrhoea and nasal blockage probably indicate AR. These symptoms may occur shortly after exposure to an offending allergen. Furthermore, the symptoms of rhinoconjunctivitis may be either seasonal or perennial. On physical examination, the clinical features may include:

- Dennie-Morgan lines (a fold in the skin below the lower eyelids);
- the allergic salute (leading to a transverse nasal crease);
- allergic shiners (dark discolouration of the skin under the eyes); and
- the presence of swollen, often hyperaemic or pale/grey inferior turbinates during anterior rhinoscopy.

In addition, other atopic features, including asthma, eczema and food allergies, may be present.[3]

In children, poor AR symptom control not only affects quality of life (QoL) significantly, but it may also lead to complications such as serous otitis media, recurrent sinusitis and sleep apnoea. Furthermore, in children with asthma, poor AR symptom control may lead to poorly controlled asthma – an important cause of repeated healthcare visits and unnecessary prescriptions for antibiotics and oral corticosteroids.[4]

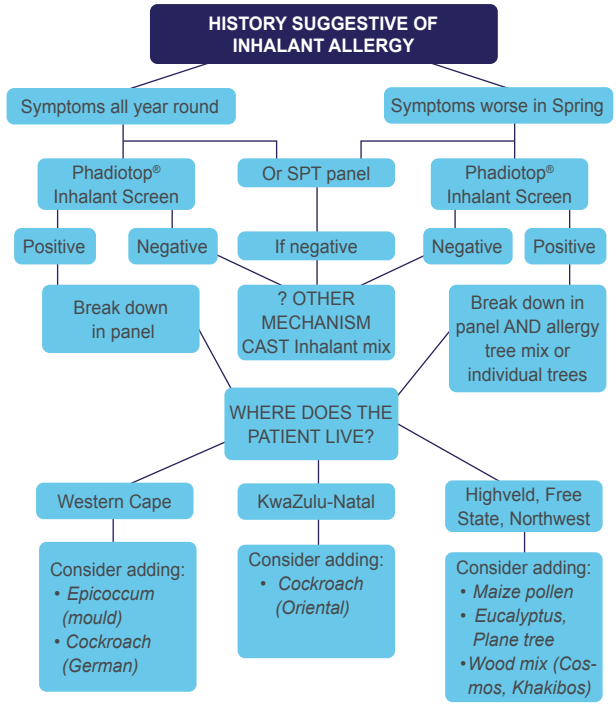

Figure 1(a): Suggested aeroallergen testing algorithm (from the SAARWG consensus document); SPT – skin-prick testing; CAST – cellular antigen stimulation test; KZN – KwaZulu-Natal[7]

Phenotypes of chronic rhinitis in children

Classifying children with chronic rhinitis into different phenotypes will not only provide better insight into the different underlying pathophysiological mechanisms (endotypes) but also contribute to a more tailored and individualised management approach. The allergy (atopy) testing currently being used in everyday allergy clinics seems insufficient in some instances, especially if local allergic rhinitis (LAR) is present. Performing a nasal allergen challenge (NAC), in addition to standard atopy testing, would be more suitable in these patients.[5,6]

Recently, by means of a stepwise allergy work-up and NACs, Prieto et al described the major phenotypes of rhinitis. Here, children with AR demonstrated sensitisation to at least one aeroallergen during NAC and a positive skin-prick test (SPT) and/or serum IgE for all NAC-positive allergens. Children with LAR had at least one positively identified allergen during NAC, but negative SPT and serum IgE tests against all allergens tested. Another phenotype mentioned was dual allergic rhinitis (DAR). These children had co-existing AR and LAR with a positive NAC and positive SPT to at least one tested allergen, and a positive NAC but a negative SPT to at least one tested allergen. Furthermore, children with non-allergic rhinitis (NAR) had a negative NAC for all the allergens tested, regardless of SPT and serum IgE results.[6]

From this study it is evident that many different phenotypes of chronic rhinitis exist – this article focuses mainly on the AR phenotype (the phenotype most encountered in children). Clinicians are also reminded that negative aeroallergen SPT and allergen specific serum IgE test results do not exclude AR.

Differential diagnosis of chronic rhinitis in children

Allergy, although common, is not the only cause of chronic rhinitis in children. The differential diagnosis of chronic rhinitis is extensive and goes beyond discussion in this article. Inborn errors of immunity (IEI), primary ciliary dyskinesia (PCD), cystic

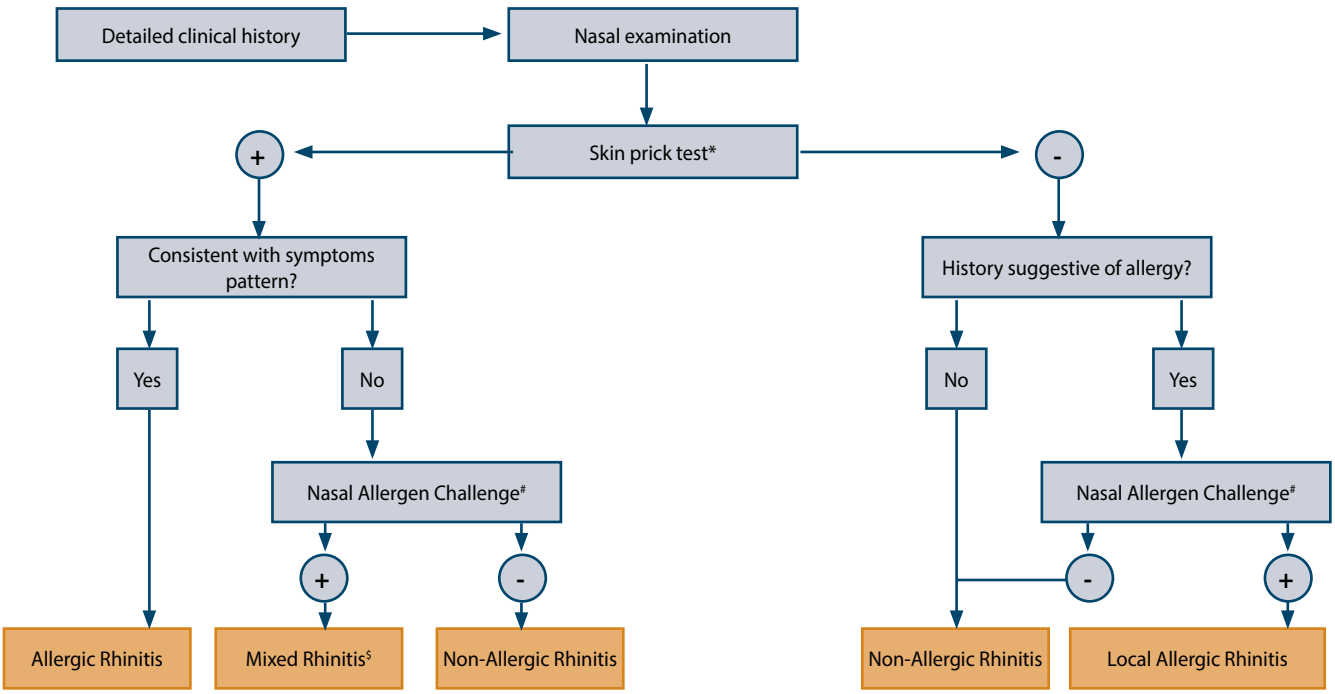

Figure 1(b): Phenotypical identification of children with rhinitis (*Alternative to SPT, serum IgE to specific allergens can be performed; #use allergen(s) that would explain symptom pattern; $mixed rhinitis implies AR and NAR co-exist in the same patient – reprinted with permission)[6]

fibrosis and a foreign body in the nasal passage are some important conditions to be considered.[7] Warning signs for general practitioners, indicating the need for early referral to a specialist, include:

- unilateral nasal symptoms;
- severe nasal obstruction (with or without obstructive sleep apnoea);
- persistent nasal symptoms in children under the age of two years;
- the presence of nasal polyps; and
- unremitting AR, despite optimal first-line treatment.

Patients with chronic AR may also present with acute exacerbations of nasal and ocular symptoms. Acute AR may necessitate treatment being escalated temporarily, over and above existing chronic AR treatment. An example would be the addition of a short course (maximum duration of five to seven days) of nasal decongestants (oxymetazoline).[3,7–9]

Aeroallergen testing in chronic rhinitis

SPT or allergen-specific serum IgE should be performed to confirm the diagnosis of AR. In addition, the importance of performing an NAC has been highlighted earlier. Sensitisation to an aeroallergen must be correlated with the patient's clinical history and symptoms. The sensitivity and specificity of SPT range from 68% to 100%, and 70% to 91% respectively.[3] Numerous medications have been shown to interfere with SPT results, mainly causing the suppression of skin-prick wheal reactions and leading to false negative result interpretation. Although no clear consensus exists on this approach, in general, stopping antihistamines for a period of three to seven days prior to SPT seems adequate.[8] However, in clinical practice many patients attending allergy clinics are using first-generation antihistamines with a shorter half-life, in which case a 48-hour wash-out period prior to testing should be advised.

The South African Allergic Rhinitis Working Group (SAARWG) has published a consensus document on aeroallergen testing. This is tailored specifically to South Africa and is based on inhalant allergens prevalent in different geographical areas of the country. As a basic 'screen', all patients with suspected AR should be tested for Bermuda grass, Rye grass, *Dermatophagoides pteronyssinus*, *Blomia tropicalis*, *Alternaria alternata*, *Cladosporium herbarum*, *Aspergillus fumigatus*, and cat and dog sensitisation. In addition, owing to the likelihood of different aeroallergen exposures of patients residing in different geographical areas of the country, region-specific aeroallergen testing is recommended. This ensures a cost-effective yet efficient investigational approach (see Figure 1(a)).

Although the SAARWG recommends the Phadiatop® test as an important initial screen in all patients with AR symptoms, it should be noted that *Blomia tropicalis* is not included in this screening panel. In South Africa, *Blomia tropicalis* has been identified as a ubiquitous aeroallergen, especially in the coastal areas of the country. For patients residing there, separate testing for *Blomia tropicalis* (apart from the Phadiatop® inhalant screen) by means of either an SPT or specific serum IgE measurement is strongly advised. The SAARWG does not recommend the testing of serum total IgE and food allergens in patients with AR, unless a specific cross-reactive syndrome (eg pollen–food syndrome) is expected – in which case, component-resolved diagnostics and newer multiplex assays (eg ISAC112/ALEX) may be of diagnostic value in these instances.[7]

Standard atopy testing may underdiagnose certain phenotypes of AR. For example, patients with LAR may indeed have negative SPTs and serum-specific IgE levels to common aeroallergens but still suffer from significant disease. Prieto et al highlight the importance of performing a NAC in addition to standard atopy testing. The authors propose a diagnostic algorithm to be used in children with chronic rhinitis, especially if discrepancies between their clinical history and SPT and/or allergen-specific IgE results exist (see Figure 1(b)). The NAC, also called the nasal allergy provocation test (NAPT), can be performed in children from five years of age.[6] The practicalities of performing this test are discussed in a separate article in this issue.

The Visual Analogue Scale (VAS)

The Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines aim to standardise AR treatment globally. These guidelines acknowledge the use of simple scoring systems to assess different symptoms of AR objectively.[10] The Visual Analogue Scale (VAS) is an easy-to- use, objective and quantitative measurement of different end points of AR symptoms that can be used during routine history-taking. It shows high sensitivity and reproducibility and correlates with more extensive symptom scoring systems – for example, the Sino-Nasal Outcome Test-22 (SNOT22) questionnaire.[11] The VAS has also been shown to correlate well with symptom outcomes from the ARIA guidelines.[12]

The VAS system can be performed by using a horizontal 100 mm long line, with patients marking the severity of a specific AR symptom themselves (0 = good (not at all); 100 = bad (very much)). Each symptom of AR can be scored individually, with a total score then summed out of 100. Scoring more than 50 indicates poor control, whereas a score of 20 to 50 indicates partial AR control. Scoring less than 20 indicates good AR symptom control.[13] Electronic versions available as downloadable mobile phone applications have also been developed.[14] The VAS not only helps to assess AR symptoms from a patient's perspective, but also provides guidelines to the clinician on appropriate management based on the severity of symptoms.

The EUFORIA guidelines and an introduction to the Emoji-VAS

The European Forum for Research and Education in Allergy and Airway Diseases (EUFOREA) is a collaboration of global key opinion leaders that aims to streamline care between patients, pharmacists and healthcare practitioners.[3,10] A novel child-friendly Emoji-VAS

scoring method was introduced in the EUFOREA guidelines; it can be used during initial clinical assessment and patient follow-up. In addition, it can be used on children from the age of six years and it is easy for them to perform themselves; or it can be done with parental assistance. Simple AR treatment outcomes – for instance, *'How are you feeling today?'* – can be assessed and are able to guide clinicians on appropriate treatment options. Each outcome (question) is subjectively scored out of 10:

- a score of more than 5 indicates uncontrolled AR symptoms;
- a score of 2 to 5 indicates partially controlled symptoms; and
- a score of less than 2 indicates well-controlled AR symptoms (see Figure 2).

Although it is currently being assessed for validity in children with AR, Emoji-VAS scoring has been used with great success during pain management in children, especially during dental procedures.[15,16]

Treatment of allergic rhinitis in children

AR treatment comprises important aspects (pillars), including patient education, practical allergen-avoidance strategies, pharmacotherapy and allergen immunotherapy. In South Africa, clinicians are guided by recommendations from the SAARWG.[7] Recently, EUFOREA, from Europe, also published a management algorithm for treating AR (see Figure 3).[3,9,10,12]

Safety first

The African continent is still considered to be part of the developing world and is often challenged by difficulties in implementing recommendations and guidelines from First World countries in Europe. For instance, in Kenya, access to safe second-generation antihistamines is restricted. Reports indicate that up to 90% of mothers administer over-the-counter cold and flu preparations containing first-generation antihistamines to children as young as three months old.[16]

Globally, the off-label use of certain medications, owing to the exclusion of children in many drug-safety studies, remains of enormous concern.[17] Serious AR medication side-effects, especially from first-generation antihistamines, have been reported. Compared to newer second-generation antihistamines, older first-generation antihistamines are also poorly researched in children.[18] In South Africa, these are frequently prescribed to the very young and are provided to patients in an uncontrolled manner (eg by pharmacies and primary healthcare clinics). For these reasons, healthcare workers and doctors are encouraged to familiarise themselves with the side-effects of antihistamines and other AR pharmacotherapies. They must also recognise that the use of first-generation antihistamines is strongly discouraged in both the SAARWG consensus document and the EUFORIA guidelines.[3,7]

Education and allergen avoidance

Adequate patient education in patients with AR has been shown to promote successful treatment outcomes.[8,11] Patients should understand the chronicity of the disease and for this reason ongoing, daily treatment should be emphasised during patient education. Apart from immunotherapy, there is no curative treatment for AR. In both the SAARWG consensus document and the EUFORIA guidelines patient education forms an important pillar of AR treatment – this usually includes education about allergen avoidance. Interestingly, the EUFORIA guidelines promote the wearing of face masks to reduce aeroallergen exposure.[3]

Implementing allergen avoidance and reduction strategies is a well-established first-line treatment modality in most allergic

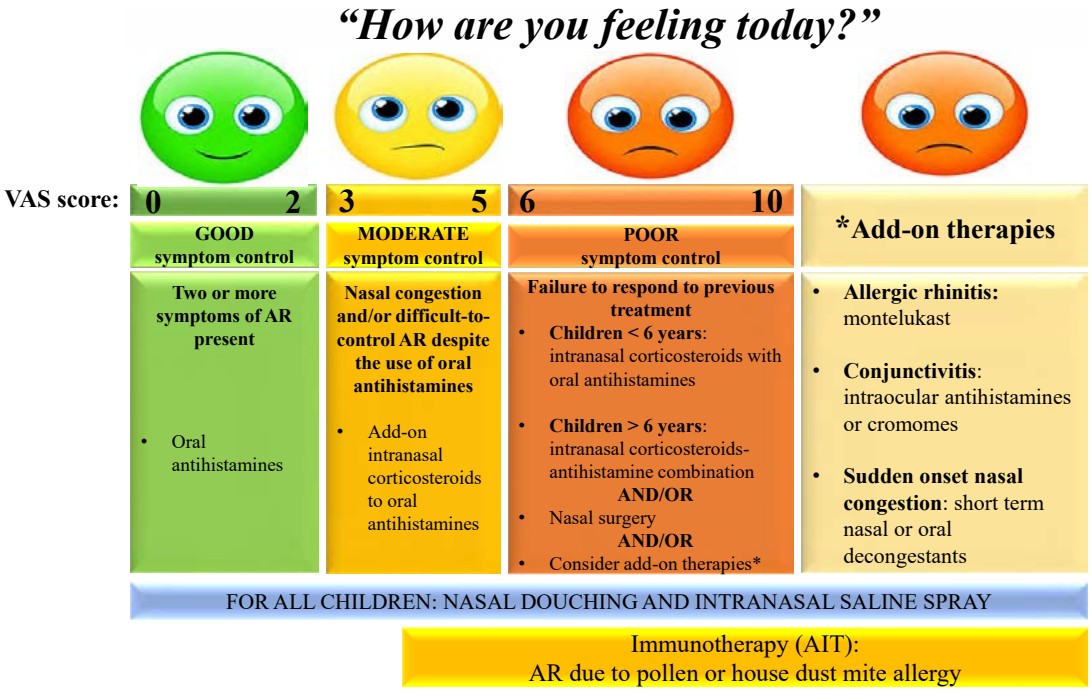

Figure 2: Management of AR in children based on the Emoji-VAS score

Table I: Comparison between the SAARWG (2015) and EUFORIA (2021) recommendations[3,7]

	SAARWG (2015) RECOMMENDATIONS	EUFORIA (2021) GUIDELINES
Intended population	• Children and adults	• Children only
Saline sprays and/or nasal douching	• Recommended for all AR and rhinosinusitis patients • Use in addition to intranasal corticosteroids (INCS)	• Universally recommended for all ages
Intranasal corticosteroids (INCS)	• Recommendation as first-line treatment for all patients with AR • Efficacious for both intermittent and persistent AR • Efficacious in addressing all symptoms (eg blocking, running and sneezing) of AR • No single molecule deemed better than the other – all more efficacious than placebo in randomised controlled trials • Systemic bioavailability (if erroneously swallowed): < 1% for fluticasone, mometasone and ciclesonide; 30–40% for beclomethasone and budesonide • Beclomethasone may suppress growth velocity. Drop-formulation has been associated with Cushing's syndrome • Safety aspects of INCS should be taken into consideration if patients are on multiple sources of corticosteroids[22]	• More effective than H1-antihistamines and leukotriene receptor antagonists • First-line treatment for moderate to severe AR • Ciclesonide, fluticasone propionate, fluticasone furoate and mometasone furoate have the least systemic bioavailability • Monitoring of growth recommended in children on INCS
Combination intranasal therapy (sprays)	• No combination antihistamine-INCS available in South Africa	• Combination antihistamine-INCS recommended for children older than six years, with difficult to control symptoms • FDA approved mometasone furoate-olopatadine combination in children older than 12 years – more efficacious than individual compounds alone
Systemic antihistamines	• First-generation antihistamines have no place in AR treatment due to unwanted side-effects • When used as add-on therapy to INCS, second-generation antihistamines are only useful when pruritis, sneezing and rhinorrhoea are predominant AR symptoms • Use as first-line therapy, only if patient is reluctant to take INCS • Maximal effect in AR symptom relief, only after two weeks of continuous use • Blood-brain barrier-crossing (up to 30%), even with second- generation antihistamines has been reported • Choice of second-generation antihistamines should be individualised. Consider pregnancy, concomitant drug use (drug interactions) and cost of antihistamine • Fexofenadine can be used from six months of age[23] and desloratadine from two years of age[24] • Should not be used to treat viral colds	• When two or more AR symptoms are present, a non-sedating oral antihistamine is advised • In adults, adding oral antihistamines to INCS, is *not* efficacious • INCS should be added to systemic antihistamines only if ocular symptoms co-exist
Nasal decongestants	• Rhinitis medicamentosa (RM) is a concern	• RM is a concern • Brief use, under specialist supervision recommended
Montelukast	• Not as monotherapy for AR • Use when predominant nasal congestion is present and if concomitant asthma exists • Not as effective as INCS and systemic antihistamines • Given as a trial for at least four weeks, before efficacy is evaluated • Combining montelukast and antihistamines is costly – this is not advised • Concerns about central nervous system and psychiatric side- effects	• Use as add-on therapy in children with concomitant asthma • Efficacy similar to oral antihistamines. Superiority above antihistamines may be genetically determined • Close monitoring recommended, especially for psychiatric side-effects
Oral corticosteroids	• Strongly discouraged in viral colds • Discourage over-the-counter formulations	• Only use if severe symptoms are present • Use under specialist supervision for brief periods • Avoid depot formulations
Antibiotics	• No role in uncomplicated AR. Only indicated when bacterial infection is suspected	• Not mentioned in the guidelines

patients.[19,20] These strategies may be costly and can be time-consuming for patients. It is therefore important that specific allergen-avoidance and -eradication strategies should be implemented only after proof has been obtained of allergen sensitisation and its clinical relevance in a specific patient. Advising blanket allergen avoidance should be discouraged. Exposure to cigarette smoking should always be avoided. For South African patients with AR, local websites can help to provide tailored and relevant education about AR (https://www. allergyfoundation. co.za). City-specific pollen counts (calendars) are also now

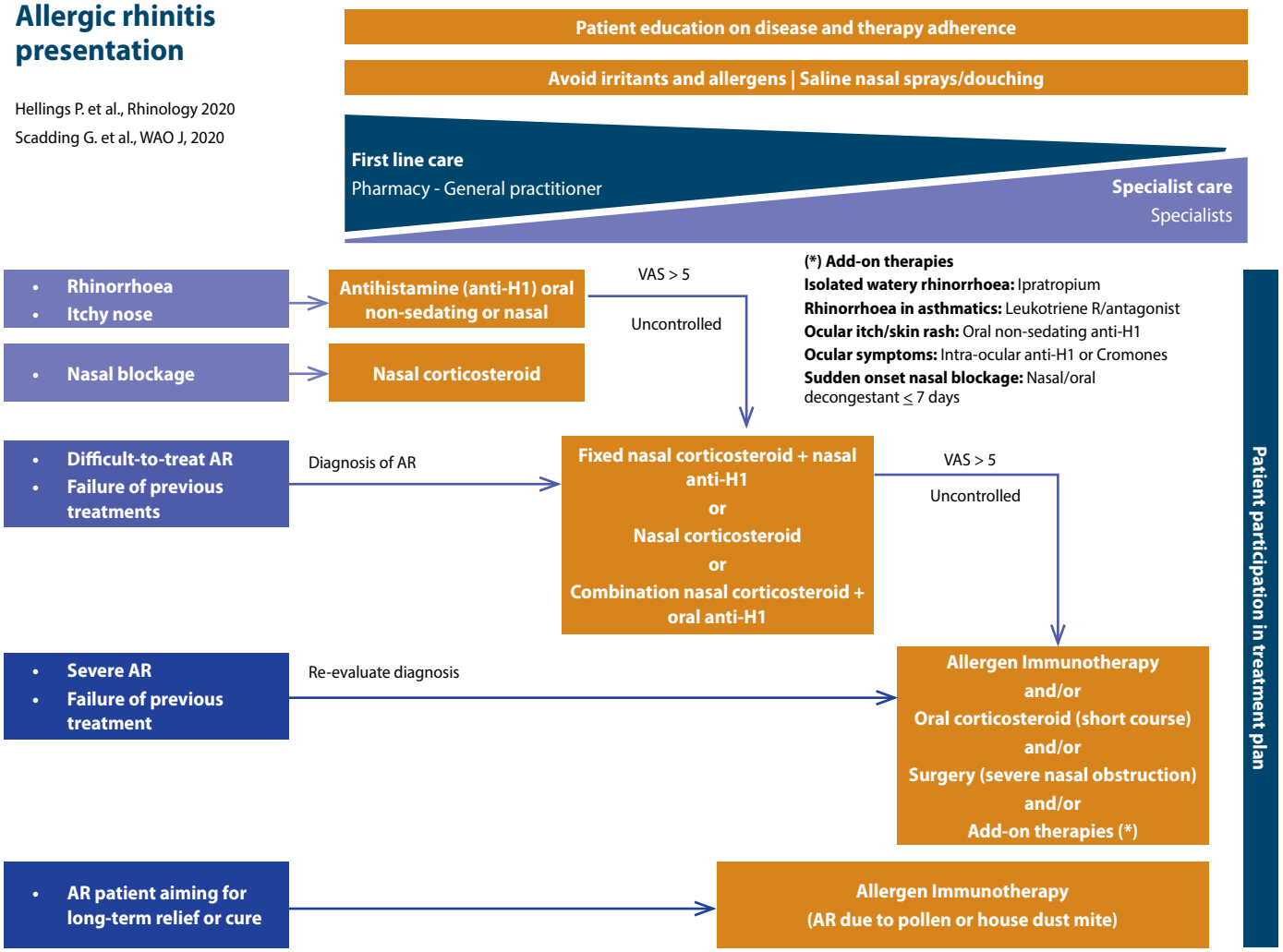

Figure 3: Management algorithm for treatment of AR based on the EUFOREA algorithm[3]

available in South Africa (https://pollencount.co.za). Once a specific aeroallergen sensitisation is known, patients should use these calendars to keep track of their relevant aeroallergen counts and manage their AR symptoms both proactively and with extra vigilance. Pollen calendars are also able to guide clinicians in the appropriate choice of immunotherapy.[21]

Pharmacological treatment of allergic rhinitis in children: is South Africa in line with European guidelines?

The partial purpose of this article is not to repeat recommendations already published in the SAARWG consensus document but to rather compare these with guidelines from First World countries in Europe. The authors of this article have summarised the major recommendations from both the SAARWG and the EUFORIA guidelines. Although relatively in line with the EUFORIA guidelines, the cost of medication and accessibility to certain treatment options are main disparities between the two sets of guidelines (see Table I).

Immunotherapy for allergic rhinitis

Aeroallergen immunotherapy is indicated in patients with an unremitting symptom history of AR (rhinoconjunctivitis) which interferes with daily activity and in the presence of proven sensitisation to one or more clinically relevant aeroallergens. It is therefore not registered as the first-line treatment of AR.[8] Conventional AR management and pharmacotherapy should be used first. It can be initiated in patients from as young as five years of age. Polysensitised patients with clear poly-allergy to different biologically related aeroallergens also qualify. It is generally recommended that immunotherapy be continued for a minimum period of three years. Furthermore, a three-year course of immunotherapy has also been shown to protect against the development of asthma in children and adolescents for up to two years after cessation of pollen immunotherapy.

Cost–utility analyses from several health economic studies have demonstrated the cost-effectiveness of immunotherapy compared to pharmacotherapy alone.[25,26]

In South Africa, both subcutaneous (SCIT) and sublingual (SLIT) immunotherapy are available.[27] These are prescribed for individual patients and administered only after South African Medicines Control Council (MCC) approval. With immunotherapy currently being the only available disease-altering treatment for patients with AR, both the SAARWG consensus document and the EUFORIA

guidelines, in line with the European Academy of Allergy and Clinical Immunology (EAACI), highlight the clinical effectiveness and the cost-effectiveness of this treatment modality in patients with allergic rhinoconjunctivitis.[3,7,26]

Difficulties in treating allergic rhinitis in South Africa

Unfortunately, the cost of and the accessibility to some AR treatment options have been recognised as substantial barriers to treating patients in South Africa optimally.[28] Here, patients are treated in either the public or the private healthcare sector. Neither of these pays for immunotherapy and therefore patients are expected to pay for it themselves. In the South African private healthcare sector AR is not regarded as a prescribed minimum benefit (PMB) and imbursement for it through medical schemes is not catered for. Furthermore, in the public sector patients often have access only to older second-generation antihistamines and still rely mostly on first-generation antihistamines. An urgent plea is therefore made to South African healthcare authorities and stakeholders to reconsider the imbursement of newer- generation antihistamines and antihistamine-corticosteroid combination nasal spray preparations. More particularly, reimbursing aeroallergen immunotherapy should be considered as a cost-effective treatment option for patients attending both the public and the private healthcare institutions in South Africa.

Conclusion

AR and rhinoconjunctivitis are extremely common in children and are often misdiagnosed as viral rhinosinusitis. Although the diagnosis of AR in children is primarily based on clinical history and physical examination, clinicians are encouraged to prove objectively patient sensitisation to common aeroallergens. This can be done by performing SPTs or measuring allergen- specific serum IgE. In addition, the NAPT/NAC is recommended as an accurate means of diagnosing newer emerging phenotypes of AR such as LAR. Allergen avoidance (including exposure to cigarette smoking) thorough patient education, pharmacotherapy and aeroallergen immunotherapy are important pillars of treatment. Recently, EUFORIA published guidelines on the diagnosis, management and assessment of AR in children. These guidelines introduced a novel child- friendly method of Emoji-VAS scoring for subjectively evaluating symptom control in younger patients. Although South African treatment recommendations for AR are largely in agreement with the EUFORIA guidelines, some differences – for example, access to certain combination medications – exist between them. Furthermore, the cost of and accessibility to especially aeroallergen immunotherapy are currently the greatest barriers to effectively managing children with AR in South Africa.

Conflict of interest

The authors declare no conflict of interest.

This article has been peer-reviewed.

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A case report on cotrimoxazole-induced Sweet syndrome – a dermatological dilemma

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Abstract

Sweet syndrome (SS) is an uncommon auto-inflammatory disorder presenting with acute pyrexia, leucocytosis and erythematous skin lesions with dense neutrophilic dermal infiltration. SS is seen as adverse reaction to some drugs, microbes and is associated with certain myeloproliferative or haematological neoplasms and is also seen with autoimmune diseases like inflammatory bowel disease, systemic lupus erythematosus, rheumatoid arthritis, etc. A female aged 43 years, came to the hospital with high fever and erythematous, pus-filled plaques and nodules on her face, neck, shoulders and extremities, after taking cotrimoxazole (antibacterial agent) in tablet form 480 mg twice daily for five days for urinary tract infection. The diagnosis of SS was arrived upon from the biopsy reports showing predominant neutrophilic infiltrate, and relevant laboratory tests. Treatment included oral prednisone (corticosteroid) and the symptoms resolved in two months.

Keywords: Sweet syndrome, acute febrile neutrophilic dermatosis, drug-induced SS, cotrimoxazole, hypersensitivity

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Introduction

Sweet syndrome (SS), also called the acute febrile neutrophilic dermatosis or Gomm-Button Disease, is a rare inflammatory dermatological disorder with typical symptoms such as rapid onset of painful cutaneous neutrophilic lesions that are tender, red, swollen and painful, erupting mostly in the upper dermis of the skin of the face, arms, neck, head, and trunk along with a rapid onset of fever and leucocytosis.[1] Dr Robert Douglas Sweet was the first person to describe this inflammatory condition in 1964 and hence named after him. Cotrimoxazole-induced Sweet's syndrome was first described in 1986.[2]

SS is an autoimmune disorder, a form of hypersensitivity developed in response to antigens like bacteria, or virus, or tumour, or even some drugs, which initiates a cascade of cytokine release. Exacerbation of lesions on exposure to sunlight (photoinduction) and appearance of new, typical skin lesions in otherwise healthy skin (Koebner phenomenon) may be the reason for local skin lesions in SS.[3] The pro-inflammatory ultraviolet B may recruit and activate more neutrophils along with enhanced release of TNF-α and interleukin-8 (IL-8).[4-6]

Up to now, only a few SS cases have been reported and generally has a female predilection with female to male ratio of 4 to 1.[7]

Case report

A female aged 43 years, presented to the outpatient dermatology department with high grade fever and erythematous, pus-filled plaques (Figure 1A, B) and nodules on the face, neck, shoulders and extremities, after taking cotrimoxazole (bactericidal and a fixed-drug combination of trimethoprim 80 mg + sulphamethoxazole 400 mg) in tablet form 480 mg twice daily for five days for urinary tract infection. Cotrimoxazole is generally the drug of choice in pneumonia, bronchitis, infections of the urinary tract, etc. Skin biopsy and laboratory tests yielded a diagnosis of Sweet syndrome. Acute-phase reactants-C reactive protein, peripheral neutrophils, leucocyte count, erythrocyte sedimentation rate (ESR) were elevated. Dense, diffused neutrophilic infiltrate in the dermis with oedema in the papillary dermis were revealed in the biopsy report (Figure 2B). The offending drug was immediately stopped (dechallenge positive). The patient was treated with oral prednisone which, after being converted to prednisolone in the liver, inhibits proinflammatory cytokine production and promotes anti-inflammatory signals. It was given in a dose of 40 mg daily

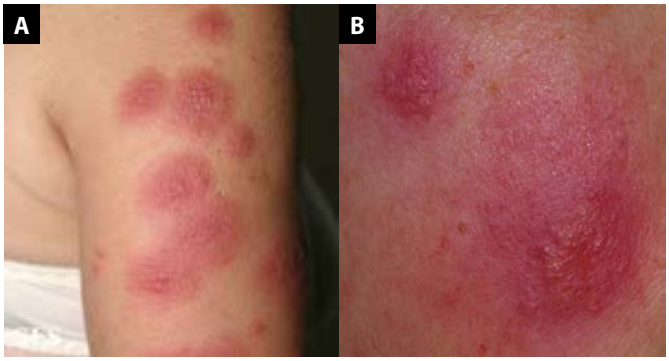

Figure 1: A - Cotrimoxazole-induced Sweet syndrome, B - Zoomed view of erythematous plaques in the patient

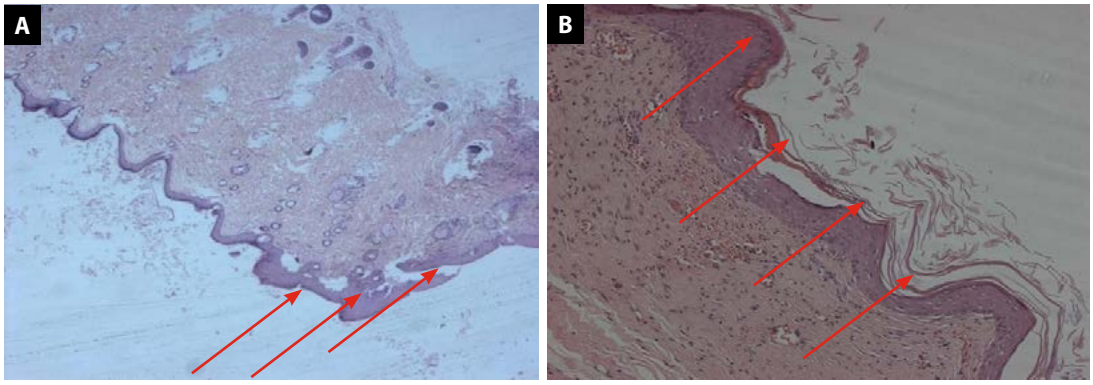

Figure 2: Histological examination
A - Complete re-epithelisation with normal epidermal layer of erupted region after treatment
B - Dense polymorphonuclear cell infiltrate in the dermal tissue

for two weeks followed by dose-tapering up to the fourth week. The patient was also given antihistamine treatment. Within two months her symptoms were resolved. Rechallenge was not done. The WHO-UMC scale is a type of causality assessment scale used in estimating the strength of relationship between drug exposure and occurrence of adverse drug reaction (ADR). According to the WHO-UMC causality assessment scale of ADR this cotrimoxazole-induced SS was found to be the probable case.

Discussion

Sweet syndrome is classified into:

- Classical Sweet syndrome (CISS – idiopathic – may be seen in conditions like upper respiratory infections, gastrointestinal infections or pregnancy (first or second trimester).[8,9]
- Malignancies-associated Sweet syndrome (MASS) – is seen in specific cancers like acute myeloid leukemia (AML).[10]
- Drug-induced Sweet syndrome (DISS) – occurs with drugs like cotrimoxazole, minocycline, abacavir, furosemide, hydralazine, ibuprofen, tretinoin or all-trans retinoic acid (ATRA) and drugs which stimulate production of Granulocyte Colony-Stimulating Factor (G-CSF). DISS occurs after exposure to the offending drug as well as re-exposure and after the withdrawal of the drug, resolution occurs with or without the use of steroids.[1]

The pathogenesis of SS is said to be multifactorial. Endogenously G-CSF levels were raised in multiple cases of SS, with elevations in serum concentrations correlating with clinical disease severity. G-CSF, a growth factor, stimulates proliferation, differentiation and maturation of leucocytes which then attaches to the upper dermis of the skin.[11,12]The exogenous G-CSF use may intensify the causative role of G-CSF in SS further as seen in drug-induced SS. Cytokines interleukin IL-17, IL-1b are involved in SS and inflammasome may be activated. Reports of rare extra-cutaneous manifestations involving the central nervous system, internal organs, musculo-skeletal system, ophthalmic manifestations like corneal ulceration, raised intra-ocular pressure (IOP) have been noted.[13-15] The most common changes in SS are raised red, pink or purplish tender skin lumps whereas Stevens–Johnson syndrome (SJS) is a rare type of severe, serious reaction of less than 10% involvement in skin and mucus membrane. Relapse may occur in around 30–50% of people with SS, especially in malignancy cases. SS is found to be mostly common in women in the age group 30–50 years and the genetic marker associated is HLA-B54.[7]

Diagnostic criteria for drug-induced Sweet syndrome[16]

1. Sudden onset of painful, tender, erythematous plaques or nodules, distributed asymmetrically.
2. Histopathological hallmark is the dense neutrophilic infiltrate in the dermis. Leukocytoclastic nuclear debris is seen interstitially, and papillary dermal oedema (Figure 2) is common. These are the two major significant findings in SS.
3. Fever – a temperature greater than 38 °C (100 °F).
4. Established temporal association between drug intake (cause) and clinical presentation (effect), or recurrence after rechallenge.
5. Dechallenge positive: temporally-related resolution of lesions after drug withdrawal or treatment with systemic corticosteroids.

Minor diagnostic criteria must include at least two out of the four following:

- Vaccination, post-infection of the upper respiratory or gastrointestinal tract often precedes SS, and may be associated with pregnancy, any inflammatory disease or certain malignancies.
- Patient's response to systemic corticosteroid therapy is excellent.
- Abnormal laboratory values at presentation (three of the following four):
  a. Erythrocyte sedimentation rate more than 20 mm/h
  b. Positive C-reactive protein
  c. More than 8 000 leukocytes per microlitre
  d. More than 70% neutrophils
- Skin biopsy may be sent to the laboratory for further evaluation and final confirmation after a clinical examination. Dense inflammatory infiltrates in the superficial dermis show poly morphonucleocytes, lymphocytes and oedema of the dermal papillae is remarkable.[17]

Treatment

If SS does not categorically fall under CISS or MASS, then it is a self-limiting condition, responding well to steroid treatment. Treating the underlying cause may resolve the symptoms of SS. In DISS, timely identification and removal of the offending agent is beneficial but must be treated systemically with the gold standard of steroid therapy. An oral prednisone course is started for two to four weeks with gradual dose weaning. To start with, a daily dose of 40–60 mg is administered. Intralesional steroid injections and topical corticosteroids may be useful if lesions are limited. In recurring SS, first-line oral systemic agents like potassium iodide, colchicine showed the same efficacy as steroids in patients suffering from systemic infections. Second-line oral systemic agents like dapsone, isotretinoin, methotrexate, doxycycline, indomethacin, chlorambucil, and cyclosporine were found to be less efficacious compared to steroid therapy. Systemic corticosteroids have been considered the gold standard for the treatment of patients with SS; in addition, treatment with topical application of high potency corticosteroids and/or intralesional corticosteroids may be effective as either monotherapy or adjuvant therapy for treating localised lesions. After initiation of treatment with systemic corticosteroids, there is a dramatic improvement of both the dermatosis-related symptoms and skin lesions.[7,18-20] Futuristic revolutionary discovery of immune-mediated pathways associated with SS may have additional implications in elucidating several other autoimmune disorders. Therapies targeting interleukin IL-17, IL-1b and activated inflammasome, adsorption apheresis of granulocyte and monocyte may be utilised as novel approaches in SS management in the future.[1] Awareness of SS and DISS among clinicians is crucially. All healthcare professionals must consider the possibility of SS to be included in a differential diagnosis in patients with fever and abrupt cutaneous lesions. As the precise aetiology of SS is still unknown, vigorous efforts must be made to explore the aetiology of SS for better diagnosis and treatment. Innovative and effective treatment strategies like targeted therapy may be potentially beneficial to such patients.

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Conflict of interest

There are no conflict of interests.

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Ethics approval and consent to participate

Ethics approval was obtained from the Institutional Ethics Committee, Santhiram Medical College and General Hospital (Ref: IEC/SRMC/2023/140). Informed consent obtained from the patient.

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The State of Hospital Pharmacy

Nhlanhla G Mafarafara

President, SAAHIP

Nhlanhla G Mafarafara

What is the ideal picture of hospital pharmacy in South Africa within the National Health Insurance (NHI) paradigm? I am sure you all have your opinion. Some based on current challenges, some based on the recent COVID-19 pandemic and some based on science.

South Africa's healthcare system needs improvement. Hospital pharmacists are eager to go beyond procurement, distribution, and outpatient dispensing, and take on more clinical roles that can improve patient care. However, public sector hospital pharmacists often lack the time to explore their clinical core due to the burden of other duties. One study quoted a pharmacist saying "*we are trained to do more than move boxes and count pills… I would love to use the clinical side of my degree. But in practice, I sadly can't seem to find the time.*"[1] In contrast, private sector pharmacists have more opportunity to use their clinical skills to improve medicines outcomes and solve public health problems.[2,3]

Pharmacists in the private sector have established ward-based pharmaceutical care services in collaboration with multidisciplinary teams (MDT). In developed countries, there has been a significant expansion of the professional service package of pharmacists which also lead to their recognition as an important part of the MDT.[4] The public sector, however, has developed numerous science-based policies, rules and regulations, including the National Digital Health Strategy for South Africa (2019-2024), Pharmacy and Therapeutics Committees (PTCs), Antimicrobial Stewardship (AMS), and Ideal Hospital, but implementation remains yet to be realised.

Why is this the reality of South Africa and many Sub-Saharan countries?

Policy formulation is lagging and implementation of action is a chronic challenge. WHO noted significant health and economic outcomes that could be achieved by aligning pharmacy best practice with national priorities such as HIV and TB. Although numerous studies exist documenting the contribution of AMS in reduction of antibiotic overuse, its positive impact on antibiotic resistance and cost savings, it is still far from incorporation as a fundamental hospital practice. Strengthening and enhancing the role of pharmacists have potential positive impact in the overall provision of care.[5] Additionally, African countries, including South Africa, suffer from a high shortage of pharmacists with increasing patient loads and an inadequate ratio of pharmacists to hospital beds/volumes especially in rural settings.

Other factors to ponder upon

Pharmacists are rarely found in executive decision-making structures in government or in hospitals. In supply chain management, however,

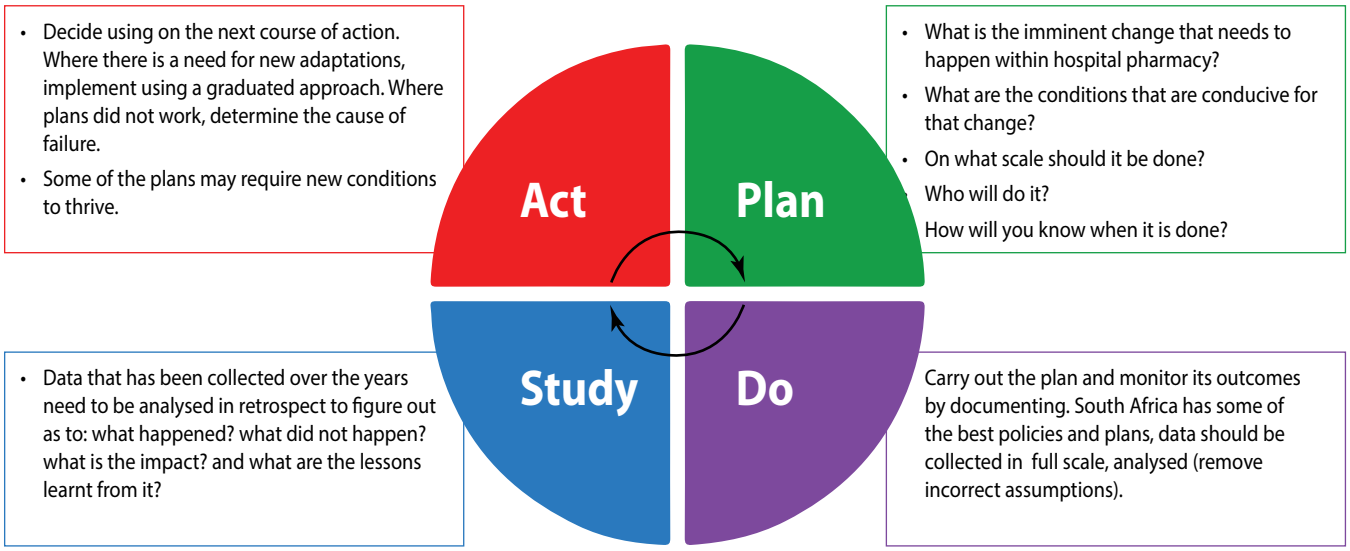

Figure 1: Plan-Do-Study-Act (PDSA) cycle

they are valued key-leaders of provincial and national structures. The private sector provides evidence of the success pharmacists experience clinically and administratively, which should be used as guidance for National Health Insurance implementation.

Fatigue and overworking pose a risk to patient safety, as some safety incidents are linked to lack of feeling well and low morale. Furthermore, misalignment of policy and political will, as well as systems inequalities, tend to prevent filling posts in the same country.[6]

Change and improvement can be introduced and implemented using known and proven methods (see figure 1)[7], both at micro (facility) and macro (national) levels. The conditions for new pharmacy practice ought to be created using existing scientific evidence for the sake of the patient. Pharmacists cannot expect the plan to happen without them directly leading the course of change in a collective health environment.

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

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This paper is based on the Life Healthcare Best Poster presentation at the SAAHIP Conference 2023

Summary

Medication errors occur frequently in a hospital setting and are often caused by inappropriate medication handling. However, systematic strategies for their prevention are still lacking.[1] Mediclinic Emfuleni Hospital decided to implement a quality improvement project (QIP) regarding the handling, storage and administering of light sensitive medication, following an audit to identify some of the medication handling errors occurring on the wards. This QIP changed how different professions at the facility, including stock controllers, pharmacy and nursing staff, view medication.

Introduction

Armand Algra

Exposure to light is a concern with numerous medications, due to the potential for photodegradation, a chemical reaction that affects stability and effectiveness.[2] Medication that has a higher risk of changing when exposed to light is referred to as "light sensitive medication" (LSM).[2] Light has the potential to alter LSMs at four stages of the medication handling process in the hospital setting: during storage, dispensing, preparation and administration.[2]

Different types of light have different potencies, frequencies, and wavelengths.[3] The three main sources of light are sunlight, fluorescent lights, and light-emitting diodes (LEDs). Even though fluorescent lights are associated with a lower risk of photodegrading LSMs, hospitals prefer to use LED lights to save on electricity and be more ecologically friendly.

In the hospital sector, LSMs should be handled responsibly. Intravenous (IV) medication has a higher risk of photodegrading, due to the refraction of light.[3] Refraction of light takes place when light moves through a liquid barrier. This would increase the contact time of light with medication molecules in a liquid dosage form, even if it has been diluted, for example when added to a large volume parenteral such as an IV fluid bag.[3] The five recommended steps for safely administering an IV LSM are summarised in Figure 1.[3]

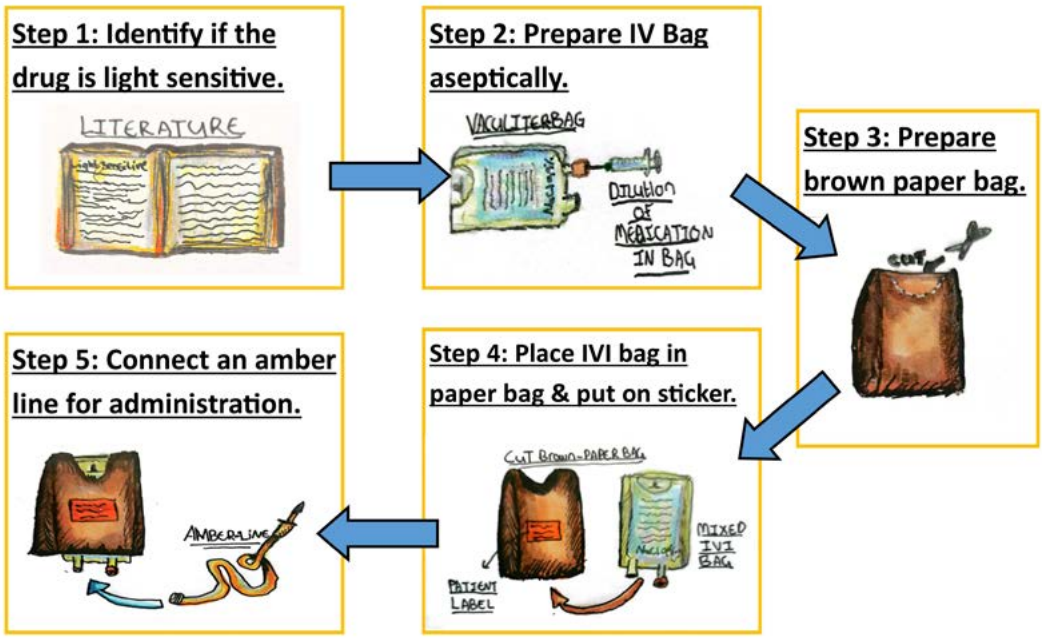

Figure 1: The 5 steps in administrating a LMS

Methods

The aim of the QIP was to ensure light sensitive medication was stored, dispensed, reconstituted, diluted, and administered correctly within the facility. The QIP was conducted through three phases:

- an observational phase;
- an intervention phase; and
- an implementation phase.

The observation phase was conducted over a three-month period, using a tick sheet to record medication- and medication-handling errors encountered during ward rounds.

The intervention phase, conducted over a one-month period, involved three separate steps:

- formal training, with pre- and post-training assessments, was provided to each of the different professions engaged in handling medications;
- formulation of procedures and policies for the handling of LSMs in the hospital; and
- ward rounds, where the pharmacist prospectively intervened with medication matters and assessed how to implement the procedures and policies developed regarding light sensitive medication within the wards and pharmacy. A one-month intervention period was used in this intervention.

The procedures and policies developed in the intervention phase addressed the following areas, after a list of LSMs used in the hospital was developed:

- storage of LSM in the pharmacy and at ward level;
- dispensing of LSM;
- handling of LSM; and
- reconstitution, dilution, and administration of LSM.

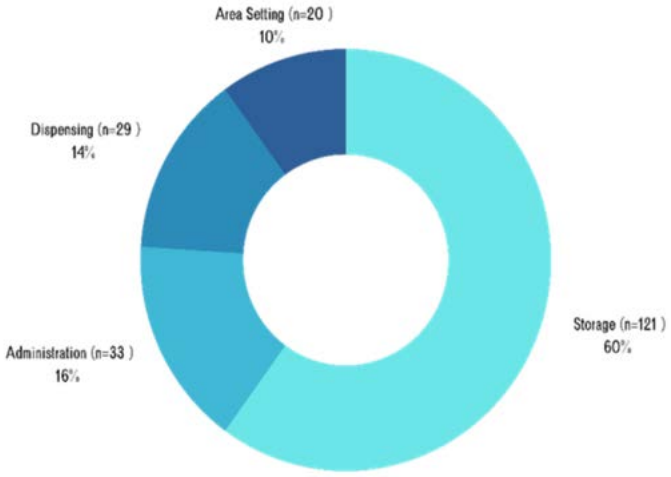

Figure 2: Total incidents of different types of incidents identified during the observation

The implementation phase, conducted over a four-month period, involved two steps:

- implementing the procedures and policies developed by means of training and formal ward rounds, assisting in making the necessary changes to daily practice (including physical changes at ward level to avoid unnecessary light exposure to any medication), and ensuring that all staff were aware of the new way of thinking regarding the handling of medication (over one month); and
- auditing the different departments to measure the success of the QIP, using an Excel audit tool, and comparing the results of pre- and post-training assessments (over three months).

Results

During the observation phase, 203 incidents were recorded in the 8 wards and pharmacy, where LSMs were handled (stored, prepared or administered) incorrectly or there was a potential for handling errors. Of the 203 incidents, 132 (65%) were identified at ward level (65%) and 71 (35%) were identified in the pharmacy. The identified incidents were grouped as follows:

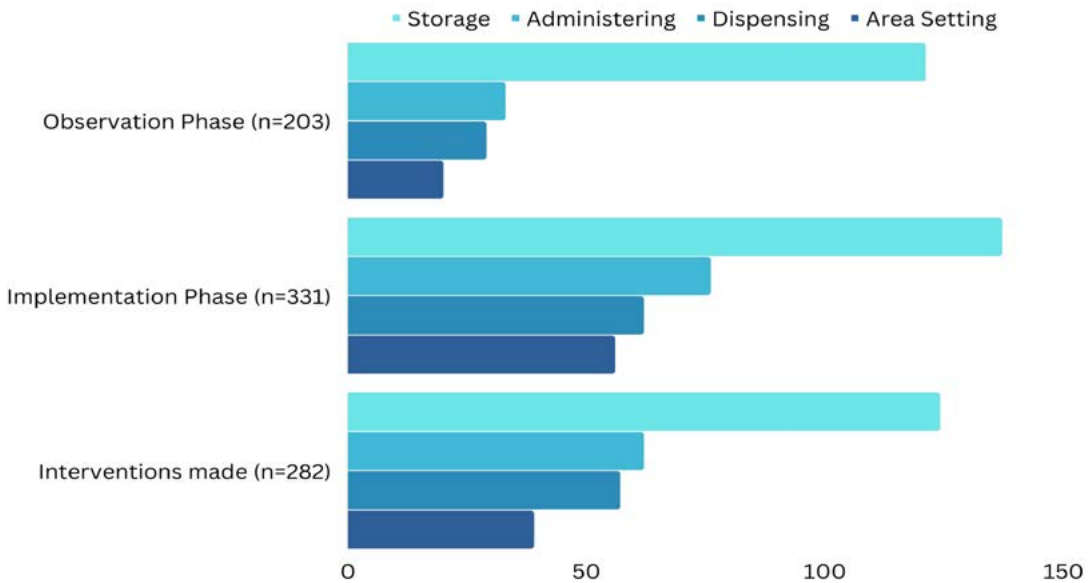

Figure 3: Different light sensitive incidents from the QIP

- storage issues;
- administration errors;
- dispensing errors; and
- issues related to the setting (ward and pharmacy).

The distribution between these groupings is depicted in Figure 2.

During the intervention phase, a total of 118 participants were engaged, comprised of 61 enrolled nurses, 42 enrolled nursing assistants, 7 stock controllers and 8 pharmacy staff members. All 118 participants received training, which focused on their units specifically. The average score for the pre-training assessment was 42%. The average score in the post-training assessment was 76%, representing a 34% increase. Based on this improvement, and the positive feedback from the participants, the training was considered to be successful.

In the implementation phase, the Excel™ audit tool was used to assess compliance with the newly developed procedures and policies. Compliance in the pharmacy was audited externally, with random assessments performed by a third party. A total of 331 observations were recorded, with the procedures and policies followed in 282 incidents. Compared with the incidents recorded in the observation phase, an 85% prevention rate of LSM-related errors was documented. The distribution of incidents during these phases is depicted in Figure 3.

Discussion and conclusion

Some of the LSM identified in the local setting are listed below, showing where in the medication handling process problems may be encountered:

- total parenteral nutrition solutions (TPN)
- metoclopramide
- ondansetron
- furosemide
- intravenous iron preparations
- morphine
- oncology medication (chemotherapy)
- insulin (when administered as an infusion or via a syringe driver)
- vitamins (including vitamin B12, vitamin B complex, vitamin K, ascorbic acid, thiamine)
- intravenous vasodilators, such as isosorbide
- antifungal, such as amphotericin B and micafungin
- hydrocortisone (only before reconstitution)
- nebulising fluids (when stored)

In addition, the tetracyclines (including tigecycline and doxycycline) are associated with the development of photosensitivity as an adverse effect.

Conclusion

In conclusion, this QIP demonstrated the essential role that the pharmacist plays in educating different healthcare professionals. The pharmacist can assist in the training of nurses, improve medication management, and prevent medication handling errors in the hospital setting. Hospital pharmacists need to engage with their peers in different professions, so that they can appreciate the pharmaceutical problems encountered in different settings, such as the wards. Only then can the problems be addressed jointly.

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Pharmaceutical Practitioner

South African Association of Community Pharmacists

SAACP AGM and Elections

Taki Kyriacos
SAACP: National Honorary Secretary

The SAACP held its 72nd AGM on Sunday, 13 August 2023. The President's Annual Sectoral Report can be viewed via this link: https://drive.google.com/file/d/1UEaTYnw0xp5-MT2SrpbJX3jF4Y3CBjMk/view?usp=sharing

During the AGM, the SAACP elected new Office Bearers. Mr Johannes Ravele was re-elected as President, Mr Jameel Kariem was elected as Vice-President, Mr Frans Landman was elected as Honorary Treasurer, and Mr Taki Kyriacos was re-elected as the Honorary Secretary. Congratulations to these members.

Awards

The Julius Israelsohn award was presented to Mr David Sieff.

About the Award

Mr JB Israelsohn, a community pharmacist, dedicated a lifetime of service to the pharmacy profession, in particular to community pharmacy. He served as Chairman of the South African Retail Chemists' and Druggists' Association for six terms between 1961 and 1972 and was awarded Honorary Life Membership of SARCDA in 1968. He was the first South African pharmacist to be elected as a Fellow of the Pharmaceutical Society of Great Britain. He was also elected to the South African Pharmacy Board, a position he held from 1976 to 1988.

In order to honour Julius for his dedicated and unstinting service to the pharmaceutical profession as a whole and the SAACP in particular, it was resolved in 1988 by the then Southern Transvaal Branch of the South African Association of Retail Pharmacists that an Award bearing his name be instituted.

About the Recipient, Mr David Sieff

We are thrilled to highlight David's extraordinary dedication to the Community Pharmacist Sector of the PSSA and his extensive involvement with the SAARP Southern Gauteng (SG) Committee. David's commitment spans decades, and his contributions have left an indelible mark on the field.

SAACP PRESCO

Since 1970, David has been a steadfast and valued member of the Community Pharmacist Sector of the PSSA. Furthermore, his involvement with the SAARP SG Committee dates back to November 1990, where he has served in various pivotal roles such as Chairman, Vice-Chairman, and Secretary. Notably, he continues to be an active member of the Southern Gauteng Branch of the SAACP.

In recognition of his unwavering dedication, David was granted Honorary Life membership of the Southern Gauteng Branch of the PSSA in February 1996. His exceptional contributions were further acknowledged through the JB Bloom Memorial Award, both in December 2000 and subsequently restored in February 2013. His outstanding achievements also include Honorary Life Membership of the CPS National and Fellowship of the PSSA National, both bestowed upon him in May 1991.

David's involvement extends beyond his local branches. He became a member of SAAHIP in April 1994 and continues to contribute as a co-opted member of the SG Branch. His passion for the history of pharmacy is evident through his membership in the SA Society for the History of Pharmacy and the Institute for the History of Pharmacy.

Throughout his journey, David has actively participated in various committees and sub-committees, focusing on communication, legal matters, student liaison, and constitutional issues. His influence has also been felt in the realms of business and public relations. His significant role in the National Pharmacy Museum's Branch Sub-Committee underscores his commitment to preserving the profession's heritage.

Notably, David's leadership shines through his role as Chairman of the 'The Golden Mortar,' the PSSA and Associated SG Branches' and Sectors' Branch newsletter, a position he has held since 1985. His dedication to fostering communication has been unwavering.

David's genuine passion for the pharmacy profession is evident in his involvement with the TPS Board of Directors of the Pharmaceutical Management Services, a company of the PSSA Southern Gauteng Branch. His initiative in addressing challenges and his positive community spirit have consistently set him apart.

As we reflect on David's remarkable journey, it's clear that his contributions have had a profound impact on the pharmacy community. His dedication to effective communication, his tireless work in various sub-committees, and his unyielding commitment to the profession's growth make him a true luminary. We are proud to celebrate David's legacy and the positive influence he continues to impart upon us all.

The President of the SAACP Mr Johannes Ravele, Mr Gary Köhn and the recipient of the Award, Mr David Sieff

The Award is made up of a gold-plated medallion displaying a bust of the late Julius Israelsohn, a certificate and a cheque to the value of R5 000

David Sieff with his daughters

Mr David Sieff with members of the SAACP Southern Gauteng Branch

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