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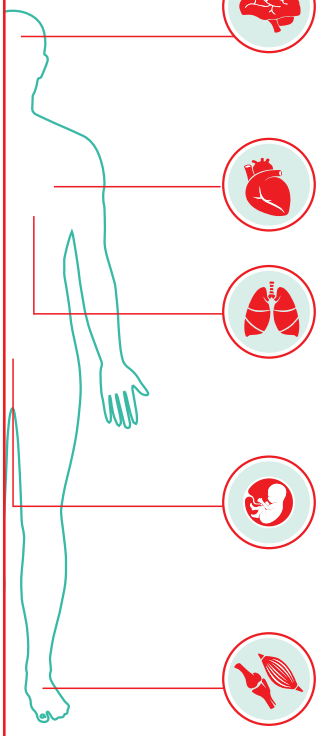
THE RACE OF THE VIRUSES IS ON! Are we ready?

Influenza was named by the Italians in the 15th century and derives from '*influence of the stars*' due to a far-reaching epidemic.[1] Today we continue striving to curb the spread of Influenza, but given the serious implications of the disease,[2] Influenza is a far cry from its namesake. It is a severe disease, causing millions of deaths globally.[1]

The challenges of Influenza control, our new normal

- Co-circulation of COVID-19 and Influenza viruses is anticipated[3]
- Symptom similarities between COVID-19 and Influenza exist[4]
- Poor uptake of Influenza vaccines[5]
- Evidenced genetic drift in virus strains[5]

Possible clinical manifestations of Influenza[6]



Neurological
Febrile convulsions*
Reye's syndrome
Meningitis/encephalitis
Transverse myelitis
Guillain-Barré syndrome

Cardiac
Pericarditis
Myocarditis
Exacerbation of CVD

Respiratory
Otitis media*
Croup*
Sinusitis/bronchitis/pharyngitis
Pneumonia
Exacerbation of chronic lung disease

Pregnancy
Increased maternal complications
Increased infant perinatal mortality
Increased risk of prematurity
Smaller neonatal size
Lower birth weight

Musculoskeletal
Myositis
Rhabdomyolysis

Adapted from Ghebrehewet S, *BMJ* 2016[6]

The underlying burden of Influenza

- High rates of school or work absenteeism[7]
- Reduced productivity[7]
- 50 % of people in South Africa annually affected by severe Influenza-associated illness require hospitalisation[8]

  Highest rates of hospitalisations are:
  - Elderly (≥ 65 years of age)[8]
  - Those with chronic conditions such as diabetes, lung and heart disease, and children < 5 years old[8]
  - Pregnant women[8]
  - Those with TB, and the immunocompromised[8]

DON'T TAKE THE RISK
VACCINATE THOSE AT RISK

VaxigripTetra®
Quadrivalent influenza vaccine
(split virion, inactivated)

GET A GRIP ON FLU

*more common in children. CVD - cardiovascular disease; TB - tuberculosis

References: 1. Barberis I, Myles P, Ault SK, *et al.* History and evolution of Influenza control through vaccination: from the first monovalent vaccine to universal vaccines. *J Prev Med Hyg* 2016;57(3):E115-E120. **2.** Uhart M, Bricourt H, Clay E, *et al.* Public health and economic impact of seasonal Influenza vaccination with quadrivalent Influenza vaccines compared to trivalent Influenza vaccines in Europe. *Hum Vacc Immunother* 2016;12(9):2259-2268. **3.** Tam JS, Shu Y. Public Health Control Measures for the Co-circulation of Influenza and SARS-CoV-2 During Influenza Seasons. *CCDC Weekly* 2021;4(2):22-26. **4.** CDC. Similarities and Differences between Flu and COVID-19. Available from: https://www.cdc.gov/flu/symptoms/flu-vs-covid19.htm. Accessed date: 28 March 2022. **5.** Argarkhedkar S, Chhatwal J, Kompithra RZ, *et al.* Immunogenicity and safety of an intramuscular split-viron quadrivalent inactivated Influenza vaccine in individuals aged ≥ 6 months in India. *Hum Vacc Immunother* 2019;15(4)973-977. **6.** Ghebrehewet S, MacPherson P, Ho A. Influenza. *BMJ* 2016;355:1-10. **7.** Kassianos G, Blank P, Falup-Pecurariu O, *et al.* Influenza vaccination: key facts for general practitioners in Europe - a synthesis by European experts based on national guidelines and best practices in the United Kingdom and the Netherlands. *Drugs in Context* 2016;5:1-18. **8.** Meyer JC, Sibanda M, Burnett RJ. Vaccination against Influenza saves lives - a 2021 update. *S Afr Pharm* J 2021;88(2):13-18.

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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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contents

SAPJ Author Guidelines

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

Aims, scope and review policy

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

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

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

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

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

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

1. This manuscript has currently only been submitted to SAPJ and has not been published previously.
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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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3. Select Author.
4. Click on CLICK HERE TO FOLLOW THE FIVE STEPS TO SUBMIT YOUR MANUSCRIPT .
5. Follow the five steps to submit your paper.

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

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A Piece of my Mind

Editorial Comment

Every now and again, a pharmacist says something that I believe really needs to be communicated. Briony Chisholm and Yolanda Harding come to mind. Although I usually only add a paragraph or two, for this edition, I believe it's appropriate to hand the rest of the page to a pharmacist who has influenced many people's careers and lives.

Lorraine Osman

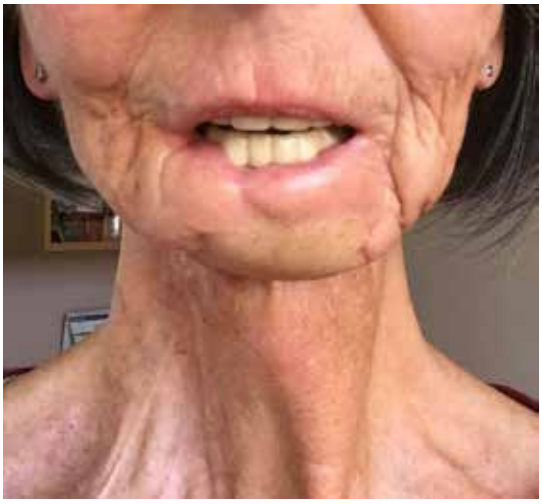
Words of wisdom and advice from Ros Dowse

25 years: A quarter century ago in late July 1997, 40 years old – that was the start of my journey – the journey no one wants. An appointment with a local doctor to look at a painful area on one side of my tongue, near the back. An ulcer – given antibacterial mouthwash and gel to soothe the pain.

Six months later, in January 1998, I finally had a biopsy. Cancer – squamous cell carcinoma (SCC) – now such a familiar acronym that has become part of my life ever since. Head and neck cancer (HNC) is a particularly vicious type of cancer – not that it kills all that fast, but it takes away the very face we present to the world and totally disrupts our lives. And oh my, is the world out there curious at the sight of anything abnormal! At this stage, after six occurrences, multiple ops which include two major, life-changing ones, I have a 'modified' face, my arm as part of my tongue, and my leg (fibula) as my jaw – ja well. But even though I now have my arm and my leg in my mouth – at least I don't have my foot in there!

Outcomes of radiation and operations come with various compromised functionalities. With an immobile tongue, no lower lip and my jaw a tad different from the original model, speech impairment is certainly a biggie for me as a former lecturer. HNC finally took me to the stage of taking my job away after my mandibulectomy in 2013. Then there's eating, chewing and swallowing – all compromised, demanding a radical change to how and what I eat.

If you think about it, the face you present to the world, and the ability to effortlessly talk, eat, drink and swallow without choking are essential to be able to move seamlessly in society and be accepted as a 'normal'. For us 'abnormals', each of these, if done 'out there' away



from our safe cocoons at home, require huge effort and resilience as we become targets of curiosity and whispers behind hands. Our lives are incredibly messy – thick mucous to be dislodged and cleared, the choking, coughing, gagging, spewing, regurgitating of food (My dog, Soxie, loves the sound – she knows she will score), dribbling, working so hard to control what, in the end, we often can't.

And sometimes disasters in public that make one never want to venture out again. So we generally eat before going out (if there are still people brave enough to invite us). In essence, we move from the centre of social life to a more marginalised, smaller, antisocial existence – and from there, we have to make big decisions about how we navigate the new landscape of our lives.

But we're a tough bunch. And we have each other, largely online, where we read about the incredible trauma experienced by fellow HNCs and support each other. If we're lucky, we have partners and families that have stuck around to support us (too many accounts out there of partners who don't), and friends to smooth out our lives and prop us up sufficiently to help us want to live. So a huge THANK YOU to all who have been part of my journey (including Soxie, my 'new life' post-mandibulectomy dog). And lastly, please all you lovely people out there, do not wait too long to check up on any niggling health issue – get it checked now!

President's Message

Pharmacy, challenged, ready, resilient

Joggie Hattingh
PSSA President

Dear colleagues and friends, bearing our conference logo in mind, I will share some of my thoughts with you.

The past few years have indeed challenged our readiness and our resilience, but as the African proverb says, "Smooth seas do not make skillful sailors".

Being challenged in life is not optional, in fact, it is what makes us grow. Our very survival depends on our ability to overcome challenges and adapt to whatever life brings. Overcoming these challenges is what makes life meaningful.

Overcoming challenge requires diversity of thought and continual interaction with others through meaningful communication! This also transpired throughout the pandemic! Those who were willing to invest time in conversations with a wide array of knowledgeable colleagues, were best positioned to inform others and to assist patients. We first overcome our own challenges, and then we can support those around us.

It would be tragic to wait until we feel ready before we confront our challenges. One could actually wait their whole life and still not be ready. Nobody ever got ready by waiting either; being ready isn't enough – we have to be prepared!

When we are prepared, we will always be ready and there will be no need to "get ready" post haste. We also must accept that we cannot make somebody be ready for what they are not ready for, and you are not obliged to wait around whilst they make up their mind.

Even when we do not feel ready at all, the first step to being ready is to start. As we move along facing the challenge, we will be more and more ready for the task at hand.

Resilience is what is required to defeat the challenge. According to Andrew Zolli, resilience is the capacity of a system or a person to maintain its core purpose and integrity in the face of dramatically changed circumstances.

It is our reaction to adversity, and not the adversity itself, that determines how things will unfold. Resilience is a very precious skill that gives us three valuable advantages: firstly, the belief that we can influence life events, secondly the tendency to find meaning and purpose in life's turmoil, and thirdly, the conviction that we can learn from life's positive and negative experiences.

It is not simply a tool to survive and overcome the unexpected, the goal of resilience is to thrive whilst doing so. Resilience should be based on our compassion for ourselves as well as our compassion for others.

Looking back at the past two years, I must admit that I am extremely proud to be part of a profession that really went all out to protect and assist our patients and our colleagues during extremely difficult times. CS Lewis once said, "Hardship often prepares ordinary people for an extraordinary destiny".

I am astounded by my fellow pharmacists who have proved themselves to be flexible in the face of change and resilient in the face of so many challenges. These attributes are choices, not talents, and if we come through our hardships a bit worse for wear, we must remember that through endurance and resilience, even the most massive characters are often seared with scars.

Many of you will attest to the fact being resilient is so much easier when we are surrounded by the right people!

May our profession continue to grow and thrive, and may the PSSA continue to serve our profession as an enabler for growth.

Complaints to SAHPRA

Every so often, the PSSA receives complaints about registered medicines being sold by unregistered persons from unregistered premises. These complaints are sent to the SAHPRA Law Enforcement division, which usually reacts swiftly. Earlier this year, the PSSA received a complaint of a different nature. This article will share some of the details of this case.

A member of the PSSA approached the PSSA, sharing a flyer from an unfamiliar company advertising a cosmetic/beauty product. The product was an injection and claimed to contain a stem cell regeneration polypeptide booster shot. Numerous claims were made with regards to the benefits of this product, including anti-ageing.

According to the Schedules to the Medicines and Related Substances Act (Act 101 of 1965) "*Injections, unless listed in another Schedule*" are a schedule 3 product and "*Biological medicines, injectable preparations thereof, when intended for human use and unless listed elsewhere in the Schedules*" are a schedule 4 substance.

If the product contained only a polypeptide booster that assisted stem cell regeneration, it would need to be registered as a schedule 3 medicine. If the product however, contained any biological material, like stem cells, it would have to be a registered schedule 4 medicine. The pharmacist who received the marketing material reached out to the South African Stem Cell Institute before contacting the PSSA. The institute reviewed the information available on the website of the company selling the product. From their research, it appeared likely that the product could contain biological material derived from frog oocytes. The product would need to be analysed to confirm its actual content.

The PSSA then reached out to SAHPRA, sharing all the information with them. SAHPRA investigated the matter, and inspectors conducted an inspection at the site. The owner of the business confirmed that the site was a home-based salon offering skin treatments. The owner is a therapist qualified in aesthetic artistry who was not aware that the product was potentially harmful and required registration with SAHPRA. The owner was instructed to cease the use and the sale of the product immediately. All promotional and marketing material was seized by inspectors. During a follow-up inspection about two weeks later, all the product and remaining marketing material on the site was seized.

Although it is concerning that products of this kind find their way onto the market, the swift reaction by SAHPRA is greatly appreciated. The pharmacy profession is encouraged to report any suspicious products to the law enforcement division of SAHPRA or to reach out to the PSSA to assist them with reporting.

FIP webinar – how can digital health support national pharmaceutical care delivery?

Substandard and falsified medicines, along with a lack of adherence to medication regimens, pose a threat to public health worldwide. It is possible to deliver pharmaceutical care services that address these challenges using digital healthcare techniques and approaches. Globally, digital health faces many challenges and concerns, despite its potential to impact pharmaceutical care.

FIP and the Global Pharmaceutical Observatory launched a new needs assessment programme entitled "How can digital health support national pharmaceutical care delivery? A regional and global assessment of priorities and challenges", with an emphasis on medication adherence and fighting substandard and falsified medicines.

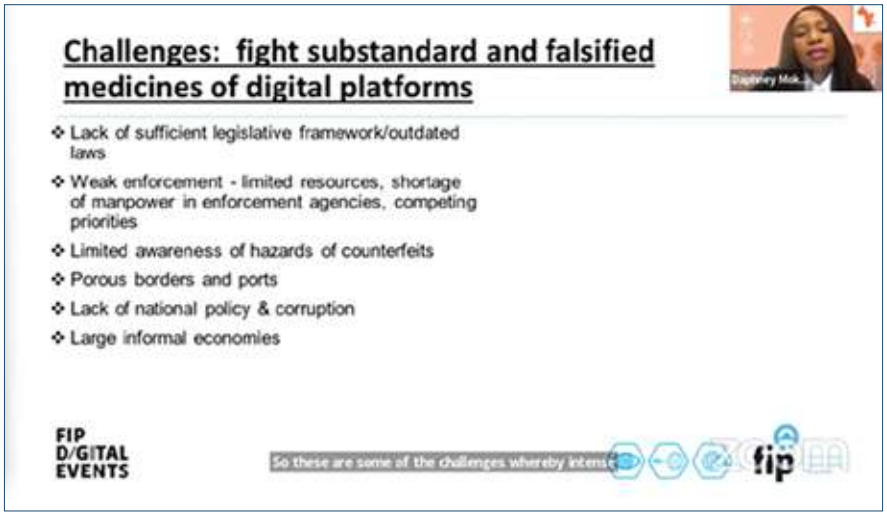
On 8 June 2022, FIP hosted an African region webinar, aiming at providing a regional and global assessment of priorities and challenges in the African region.

FIP facilitated a regional discussion about ongoing digital health interventions or solutions that detect, report, and act against false or substandard medicines, and how to facilitate patient adherence, as well as the challenges leadership bodies and nations face in implementing digital health solutions in pharmaceutical care delivery in Africa.

South Africa was represented by two speakers.

1. Brent Sin Hidge of the PSSA YPG group and a hospital pharmacist at Netcare Blaauwberg Hospital in Cape Town took part in a panel discussion about "*Digital health to support patient adherence*". He explained the barriers South Africa faces to integrate and mobilise digital health interventions and approaches in pharmaceutical care services to support medication adherence.

Brent Sin Hidge



2. Daphney Mokgadi Fafudi, the Head of Regulatory Compliance at SAHPRA, spoke about digital health to fight substandard and falsified medicines. Her presentation dealt with the prevention, detection and response to substandard and falsified medicines. She explained that SAHPRA collaborates with other law enforcement and regulatory bodies in South Africa, the African region and internationally, as well as international bodies like Interpol, that help each other to fight substandard and falsified medicines. Digital platforms selling these products are especially problematic and are often transnational.

SAHPRA webinar: a conversation on the dangers and abuse of codeine-containing medicines

On 21 June 2022, SAHPRA hosted a webinar on codeine-containing medicines. The main focus of the webinar was to unpack the dangers of irresponsible behaviour and abuse of codeine-containing medicines in South Africa. Speakers on the panel were from the South African Pharmacy Council, SAHPRA, the South African Narcotics Enforcement Bureau in SAPS, the South African Network of People who Use Drugs (SANPUD) and the PSSA. The panellists shared their knowledge, experience, and expertise to begin this important conversation focusing on the:

- Dangers of abusing codeine-containing medicines
- Illicit dispensing of codeine-containing medicines
- Roles of the various bodies in curbing unethical and dangerous practices

The PSSA was represented by Dr Mariet Eksteen from PSSA National Office.

Classifieds

Classified advertisements may be-mailed to sandy@medpharm.co.za. The placement of classified advertisements is offered as a free service to members and subscribers. Advertisements will be placed for three consecutive months, if space is available. Advertisements longer than 30 words will be edited.

The power of volunteering: highlights from the 2021/2022 Steering Committee's term!

Introduction

Volunteering may be defined as a voluntary act of a person or group of people who give their time and labour freely for community service. This definition provides an insightful view of volunteering, particularly with respect to the mention of "community service."

When considering this concept in relation to the outgoing Steering Committee's efforts over the past year, the reflective question arose:

"Did we serve our community?"

The answer is simplistic, yet complex – Yes, we served our community (PSSA). However, one always feels that more time could have been dedicated to various tasks. This question is one which all volunteers should consider when reflecting on their work.

The outgoing YPG Steering Committee has both continued the fastidious labours of their predecessors and brought forth a new momentum in the group. Duties were performed with new responsibilities arising and expectations were exceeded.

Left: Alex Wehmeyer (Public Relations Officer)
Middle: Nicole Keuler (Chair)
Right: Brent Sin Hidge (Project Coordinator)

Successes

The outgoing Steering Committee achieved much during their tenure. With support from friends, family and colleagues both within and outside the profession, various goals and dreams could be realised.

These include:

- Development and launch of the PSSA Mentorship Programme
- New YPG logo
- YPG history booklet development
- Health day awareness campaign
- New YPG newsletter design
- FIP YPG collaboration
- PSSA social media guide development
- Promotion of PSSA membership benefits

Closing words

With our term coming to an end, we as the outgoing YPG Steering Committee would like to give a special word of thanks to all those who supported us during our journey.

We wish the incoming committee all the best with the path ahead. We hope you will continue to showcase the vibrancy and aptitude of young pharmacists in South Africa.

In the kind and informative words of the long-serving PSSA stalwart, Lorraine Osman: "Don't disappear!"

Words of wisdom from the outgoing committee:

"Volunteers don't get paid, not because they are worthless, but because they're priceless"

~ Sherry Anderson

Why hypertonic saline?

According to medical research, hypertonic saline solutions may play a big part in eradicating viruses and bacteria that enter the body through the nose. With a higher salt quantity in the product than what is in your body, hypertonic saline is more effective at drawing fluid from the inflamed, swollen lining of the nose, sinus, larynx, and bronchi to help open your airways and thin mucus, which could help to reduce the ability of a virus to attach itself to the membranes and reduce the risk of infection.

Kuraflo saline solutions

With the ***Kuraflo Hypertonic Saline Solution*** range of products, you can choose to **nebulise**, **spray,** or **nasal rinse**. We aim to help you *breathe better* in a more natural, effective, and safe way.

Whatever the choice, Kuraflo is safe to use as a preventative product or to help treat symptoms when you are sick.

- Kuraflo **3% Nebulising Solution** will help reduce swelling in the larynx, trachea, and bronchi in conditions like croup, bronchitis, allergies, dry coughs, colds & flu, and airway irritation.
- Kuraflo **1.5% Paediatric Spray** is safe for kids under 12 years and still very gentle on the nasal cavities in congestion and infection, colds & flu, nasal allergies, hay fever, and creche syndrome.
- Kuraflo **3% Adult Spray** is for children over 12 years and adults and assist in pregnancy rhinitis, swelling from allergens or bacteria, post-nasal drip, congestion, and infection.
- Kuraflo **Nasal Rinse** can be mixed at either 1.5% or 3% and are safe for any age. Nasal rinsing is still one of the best methods for severe infections and alleviating congestion, as well as using it as a postop treatment for cleansing.

Mesh vs jet nebuliser

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

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

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

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

It is portable and can be used anywhere since most are battery-operated.

Kuraflo mesh nebuliser

- Up to 7 000 laser-drilled holes (more than most mesh nebulisers) for a finer mist, better absorption into the lungs, and 4–10 minute nebulising time
- Clinically tested with most (saline & prescription) medication
- Guarantee of a zero broken mesh membrane
- 30° slant in the medication chamber for better flow onto the mesh membrane
- The safety switch automatically switches off the device if it falls over or is empty
- USB cable to charge (included)
- Rechargeable lithium battery (included)

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Breathe Better

Clear more mucus and phlegm with **3% hypertonic saline**

With a higher salt quantity in the product than that of the body, hypertonic saline draws fluid from the inflamed, swollen lining of the nose, sinuses, larynx and bronchi to help open the airways.

Medical research shows that hypertonic saline may play a huge part in the eradication of viruses that enter the body through the nose. Using hypertonic saline daily keeps the nasal passages clean and thins mucus, which could help reduce the virus' ability to attach itself to membranes.

Kuraflo® 1.5% Paediatric Nasal Spray is suitable for children from 1 month to 12 years and **Kuraflo® 3% Adult Nasal Spray** is safe for 12 years and older. It will help open up the nasal cavities and thin the mucus to help patients *Breathe Better.*

The **Kuraflo® 3% Nebulising Solution** will help bring down the swelling in the larynx, trachea and bronchi to help bring quick relief, especially for patients with croup or bronchitis.

All the **Kuraflo®** Saline solutions are safe for use on a daily basis as a preventative product to wash airways clean and help protect against infections, hay fever and allergies.

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Paediatric asthma

R Green,[1] K Outhoff[2]

[1] Professor, Head of Department Paediatrics and Child Health, and Chair of School of Medicine, University of Pretoria, South Africa
[2] Associate Professor, Department of Pharmacology, University of Pretoria, South Africa

Corresponding author, email: kim.outhoff@up.ac.za

Abstract

Childhood asthma has been with us for many years, and prevalence has been increasing. Asthma is the fifth most common killer in our country, and although it may not kill as many people as infectious diseases, the quality of life of an asthmatic may be seriously impaired, leaving a child or adult with compromised lung health that never goes away. The diagnosis of asthma, which is characterised by variable expiratory airflow limitation, is primarily based on recurrent cough and wheeze. Asthma management should be personalised, and long-term asthma management involves assessing, adjusting and reviewing treatment response. Medication should be titrated up or down for individual patient needs.

Keywords: paediatric asthma, inhaled corticosteroids, long-acting beta$_2$-agonist (LABA), short-acting beta$_2$-agonist (SABA)

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Childhood asthma has been with us for many years, and sadly, has been increasing in prevalence. Although the focus has been on AIDS and TB pandemics in Africa, asthma is still common (or more common), and yet little attention is paid to it, probably because many believe that asthma is not serious or severe, and that few people die from this respiratory illness. These are myths. Asthma is the fifth most common killer in our country and although it may not kill as many people as infectious diseases, the quality of life of an asthmatic may be seriously impaired, leaving a child or adult with compromised lung health. This never goes away. Activities, sleep and school attendance are affected, causing additional stress to asthmatic children, their parents, families and carers. In addition, the term "mild" asthma may lull one into a false sense of security; any asthma may be complicated by severe acute exacerbations, and it is sobering that up to two-thirds of asthma deaths occur outside of medical facilities.[1] The diagnosis and management of asthma, therefore, require strengthening to optimise outcomes and improve health.

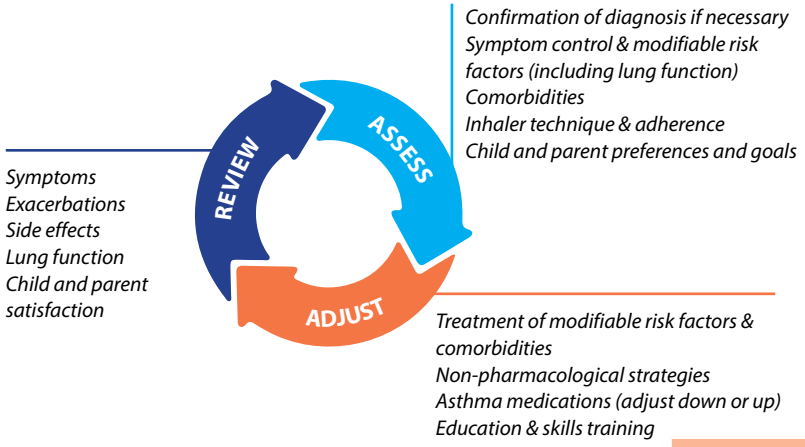
The diagnosis of asthma, which is characterised by variable expiratory airflow limitation, is primarily based on recurrent cough and wheeze, which may occur on a broad clinical spectrum that also includes breathlessness and chest tightness, induced by reversible airflow obstruction, airway inflammation with eosinophilia and/or infection. A third of children have had a wheezy illness by their third birthday, and these are mostly caused by viral triggers such as bronchiolitis and laryngotracheobronchitis. Far less commonly, functional (e.g. cystic fibrosis, gastro-oesophageal reflux disease) and structural (e.g. TB lymphadenopathy, congenital) abnormalities may cause wheeze in children under six years of age. That said, symptoms start in the preschool years in 80% of patients diagnosed with asthma.[2] However, the term wheeze is often misclassified – there is no data on sensitivity or specificity of the term 'wheeze' – and control of asthma symptoms is correlated best with composite scores of symptoms rather than wheeze.[3] An audible wheeze occurs late in airway obstruction. Cough correlates with lung function and atopy in preschoolers, similar to, and independent of, wheeze.[4]

Diagnosis of asthma in a preschool child relies on the typical history and examination, as well as demonstration of reversibility such as an FEV_1 increase > 12% with a bronchodilator or an FEV_1 decline > 15% during an exercise challenge, diurnal variation of PEF > 20% with twice-daily readings or a positive methacholine challenge test. The role of FeNO is controversial. Evidence strongly suggestive of asthma includes activity-induced cough or wheeze, cough at night, and symptoms persisting after the age of three years. Other symptoms suggestive of asthma include absence of seasonal variation, symptoms worsening with certain exposures, colds repeatedly going to the chest, concomitant rhinitis, eczema or food allergies, a family history of allergies and a positive response to a bronchodilator or a six- to eight-week therapeutic trial of an inhaled corticosteroid (ICS) such as beclomethasone, fluticasone or budesonide.[5] Wheezing more than once a month may also be suggestive of asthma, although the evidence for this is weaker.

Personalised long-term asthma management involves assessing, adjusting and reviewing treatment response. Medication should be titrated up or down for individual patient needs. The 2022 updates of the Global Initiative for Asthma (GINA) guidelines recommend that a low-dose ICS be taken whenever a short-acting beta$_2$ agonist (SABA) such as salbutamol is used in children aged 6–11 years with mild asthma.[6] This is the preferred controller combination, used to prevent exacerbations and to control symptoms. Daily low-dose ICS may be considered an alternative, although the evidence for this approach is less rigorous (Figure 1). Should the asthma require Step 2 treatment, the evidence supports daily low-dose ICS. Alternatives include a daily leukotriene receptor antagonist.[6]

Children 6–11 years

Personalised asthma management:
Assess, Adjust, Review



Asthma medication options:
Adjust treatment up and down for individual child's needs

	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
PREFERRED CONTROLLER to prevent exacerbation and control symptoms	Low ICS taken whenever SABA taken	Daily low dose inhaled corticosteroid (ICS) (see table of ICS dose ranges for children)	Low dose ICS-LABA, OR very low dose* ICS-formoterol maintenance and reliever (MART)	Medium dose ICS-LABA, OR low dose† ICS-formoterol maintenance and reliever therapy (MART). Refer for expert advice	Refer for phenotypic assessment ± higher dose ICS-LABA or add-on therapy, e.g. anti-IgE
Other controller options	*Consider daily low dose ICS*	*Daily leukotriene receptor antagonist (LTRA), or low dose ICS taken whenever SABA taken*	*Low dose ICS + LTRA*	*Add tiotropium or add LTRA*	*Add-on anti-IL5, or add-on low dose OCS, but consider side effects*
RELIEVER	*As-needed short-acting beta$_2$-agonist (or ICS-formoterol reliever for MART as above)*				

** Very low dose: BUD-FORM 100/6 mcg*
† Low dose: BUD-FORM 200/6 mcg (metered dose)

Figure 1: Personalised management for children 6–11 years to control symptoms and minimise future risk

BUD-FORM – budesonide-formoterol, ICS – inhaled corticosteroid, LABA – long-acting β_2-agonist, LTRA – leukotriene receptor antagonist, MART – maintenance and reliever therapy, OCS – oral corticosteroid, SABA – short-acting β_2-agonist[6]

In this 6–11-year age group, reliever medication typically includes an as-needed SABA (salbutamol) or an ICS-formoterol reliever, which forms the cornerstone of maintenance and reliever therapy (MART). Although formoterol is a long-acting beta$_2$ agonist (LABA) with a duration of up to 12 hours, it has a quick onset of action, typically within two to three minutes. Budesonide is the low-dose ICS typically used in combination with formoterol.[6]

Adolescents from 12 years of age are treated similarly to adults, i.e. with a low-dose ICS-formoterol combination to relieve acute symptoms or prior to exercise if required. GINA no longer recommends SABA-only or LABA-only treatment in adults and adolescents because of the increased risk of rebound exacerbations.[6]

A retrospective multinational 24-country observational study of 8 351 asthmatics (> 12 years) recently demonstrated an association between high SABA prescriptions (> 3 canisters/year) and poor asthma control, including higher rates of acute exacerbations, across a wide range of healthcare settings and asthma severities, providing support for initiatives to improve asthma morbidity by reducing SABA overreliance.[7] Targeting the inflammatory component of asthma with a corticosteroid is a rational approach to curtailing unopposed SABA monotherapy.

The 2021 South African childhood asthma guidelines recommend that in children under 11 years who have an upper or lower respiratory tract infection triggering a wheeze (with no wheeze between infections), a 7–10 day course of low dose ICS be taken to complement the as-needed SABA. If asthma is moderate to severe and persistent in children over six years, daily ICS-formoterol in a single inhaler is advised for reliever and controller therapy.[5] Inhaler devices include a pressurised metered-dose inhaler (pMDI) and spacer with a face mask for the under fours, a pMDI and spacer with a mouthpiece for the four- to six-year-olds, and a dry powder inhaler, or a pMDI with spacer and mouthpiece or breath-actuated pMDI for children over six years.[8]

Early, predictive symptoms of exacerbations in young (under five-year-old) children include increased night cough, lethargy, impaired feeding and reduced response to SABA reliever therapy. Symptom deterioration may risk the child's health and prompt an urgent visit to the doctor. When assessing a distressed child with acute asthma, it is most useful to monitor oxygen saturation. If O_2 sats remain < 92% on room air, despite a total of approximately 6–12 puffs of inhaled SABA, the child should be admitted for further treatment, which often includes systemic corticosteroids. For children under five years, this equates to two separate puffs

repeated three times at 20-minute intervals, while for children six years and over, 4–10 puffs at 20-minute intervals for the first hour. Other symptoms warranting admission for young children include an inability to speak or drink, a respiratory rate > 40 breaths/minute or cyanosis. A chest X-ray is not required in a clear diagnosis of bronchiolitis, and there is no need for routine blood tests. However, the diagnosis should be reconsidered, and investigations are required if there is lethargy, severe tachycardia, high temperatures, and/or seizures. Nasal prong oxygen is a cornerstone of acute asthma treatment. Antibiotics, nebulised agents including bronchodilators, adrenaline, steroids or hypertonic saline, oral steroids or chest physiotherapy are not usually required.[6]

Conclusion

As asthma is the most common chronic disease in childhood, it is important that diagnostic skills and treatment approaches are honed. Although acute exacerbations usually require prompt and repeated SABA administration, the move away from chronic SABA reliever monotherapy to a low dose ICS-rapid onset LABA combination may ultimately improve the health of children and save more lives.

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An overview of muscle pain

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Abstract

Muscle pain, also known as myalgia, is most commonly associated with sprains or strains. It frequently presents as redness at the site of injury, tenderness, swelling and fever. Muscle pain may occur as a result of excitation of the muscle nociceptor due to overuse of the muscle, viral infections or trauma. The most important endogenous substance released in response to the damaged tissues or nociceptor nerve endings in regards to muscle pain is adenosine triphosphate (ATP). Optimal pain management involves a combination of non-opioid, opioid analgesics, adjuvants, as well as non-pharmacological strategies. Non-opioid analgesics include paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, which are indicated for mild to moderate pain. Moderate to severe pain requires opioid analgesics. This article provides an overview of muscle pain, the management and treatment thereof.

Keywords: muscle pain, myalgia, sprains, strains, analgesics, opioids, NSAIDs

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Key summary points

- Muscle pain, known as myalgia, can be in one targeted area or across many muscles, occurring with overexertion or overuse of these muscles.
- Pain can be classified as acute or chronic pain and further categorised as nociceptive or neuropathic.
- Causes of muscle pain include stress, physical activity, infections, hyper- or hypothyroidism.
- Sprains and strains are the most common types of muscle pains.
- Optimal pain management involves utilising a combination of non-opioid, opioid analgesics, adjuvants and non-pharmacological strategies.

Introduction

Muscle pain, medically known as myalgia, can be described as pain that originates in any muscle of the body. The pain can be in one targeted area or across many muscles, usually occurring with overexertion or overuse of these muscles.

"*Pain, like love, is all consuming: when you have it, not much else matters, and there is nothing you can do about it. Unlike love, however, we are actually beginning to tease apart the mystery of pain.*"[1]

Myalgia may also occur without a primary trauma and this is frequently associated with a viral infection. The severity of pain may range from mild to severe, depending on the cause thereof. It can typically be described as cramping and aching. Signs and symptoms associated with muscle pain include redness at the site of injury, tenderness, swelling and fever.[2]

Classification of pain

Pain is classified according to its duration and pathogenesis. Depending on the duration of pain, pain can either be classified as acute or chronic.

Acute pain

This type of pain usually arises after obvious tissue damage and is, therefore, nociceptive in nature. The pain can be clearly located and resolves upon healing. It has a protective nature as it distinctly warns individuals about harmful situations.[3]

Chronic pain

Chronic pain usually persists from months to years. The intensity of the pain no longer correlates with the causal stimuli as there are changes to nerve function and transmission. The pain loses its protective and warning signs and thus serves no purpose.[3]

This pain can further be classified as either nociceptive or neuropathic.[4]

Nociceptive pain

This is known as a very high threshold pain that is activated in the presence of stimuli. It is the normal physiological pain that is associated with a warning signal that something is threatening the person's bodily tissues. It is felt when a person comes into contact with a stimulus, i.e. hot, cold or sharp. Nociceptive pain acts as a physiological protective system and signals when there is impending tissue damage. It requires immediate attention and action, like pulling your hand off a hot plate within an instant. Sprains and/or strains, broken bones, lower back pain from disc disease or injury, and burns are examples of nociceptive pain.[1,4,5]

Neuropathic pain

This pain is considered to be maladaptive, and is a disease state of the nervous system. This type of pain occurs after there is damage to the nervous system. It is experienced due to transmission of pain signals in the absence of actual tissue damage or inflammation, like fibromyalgia, tension headaches and irritable

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bowel syndrome. This pathological pain occurs when there are heightened sensory signals in the central nervous system and a low threshold of pain.[1,4,5]

Causes of muscle pain

Muscle pain can be caused by stress, tension or physical activity. Some medical conditions known to cause muscle pain include:[6-10]

- Infections
- Hyper- or hypothyroidism
- Hypokalaemia
- Autoimmune conditions, e.g. lupus
- Side effects of certain medications (i.e. the statins)

Pathophysiology of muscle pain

Muscle pain may occur as a result of excitation of muscle nociceptors due to overuse of the muscle, inflammation and/or trauma. When the impact has occurred, endogenous substances are released in response to damaged tissues or nociceptor nerve endings. Some of these substances include:[11]

- Potassium ion
- Prostaglandin E_2
- Bradykinin
- Serotonin
- Neuropeptides, e.g. substance P
- Somatostatin
- Adenosine triphosphate

Of all substances released, the most important one involved in muscle pain is adenosine triphosphate (ATP) which is released from muscle cells at high concentrations after damage to the muscles. The increased levels of substances released from the damaged tissues stimulate the nociceptors directly. The pain experienced during movement of these damaged tissues is as a result of the low threshold of sensitised muscle nociceptors.[11-13]

In the case of muscle inflammation, the level of substance P and nerve growth factor (NGF) increases, which in turn leads to hyperalgesia, known as increased sensitivity to painful stimuli in the affected muscle.[11,13]

Sprains and strains are the most common types of muscle pain and are especially frequent in the elderly. Sprains occur as a result of overstretching of the ligaments. This can be caused by the twisting of joints. The most regularly affected parts of the body are the ankles and wrists. This is usually followed by pain, swelling and, at times, bruising. Strains, on the other hand, are the overstretching of muscles or tendons.[4,14]

Management of muscle pain

Non-pharmacological management

The non-pharmacological treatments for muscle pain are illustrated in Figure 1.

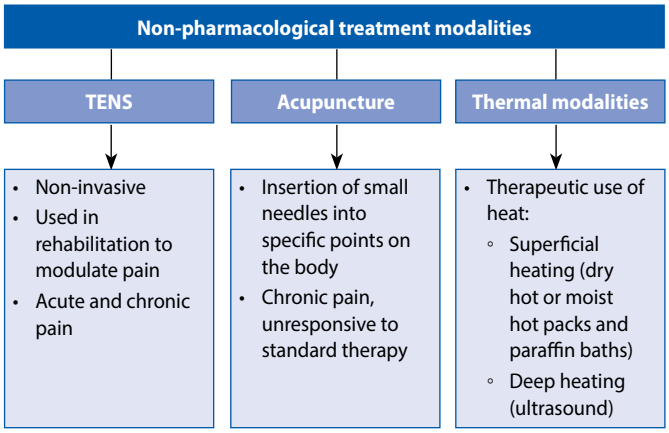

Figure 1: Non-pharmacological treatment of muscle pain
TENS – transcutaneous electrical stimulation

Treatment modalities include the following:

- *Transcutaneous electrical stimulation*

Transcutaneous electrical stimulation (TENS) is a non-invasive procedure used in rehabilitation to modulate pain.[15] Electrical currents are delivered through the skin to activate central inhibitory pathways, decreasing central excitability. Activation of the descending inhibitory pathways from the midbrain and brainstem leads to inhibition of the nociceptive neurons in the spinal cord. This is used for acute and chronic pain.[16,17]

- *Acupuncture*

Acupuncture is a traditional Chinese-based therapeutic method which involves the insertion of small, solid needles into specific points in the body in order to improve health or modify painful states.[18] There are several postulated mechanisms of action. Acupuncture is indicated for chronic pain which is unresponsive to standard therapy. Acupuncture may work via the same mechanisms of other complementary therapies (placebo, diversion etc).[19]

- *Thermal modalities*

Thermotherapy is the therapeutic use of heat, usually greater than that of body temperature, applied to the body.[20] Thermal modalities are classified as superficial thermotherapy (the application of a device that is used primarily to heat structures to 1 cm deep), and deep thermotherapy (the application of a device that causes a tissue temperature rise at 3–5 cm deep). Superficial heating modalities include; dry-hot packs, moist-hot packs and paraffin baths. Deep heat modalities include therapeutic ultrasound.[20]

Pharmacological management

Optimal pain management involves utilising a combination of non-opioid, opioid analgesics, adjuvants and non-pharmacological strategies. The approach must be adapted such that it is possible in resource-limited areas as well. Treatment guidelines should therefore consider the acute and chronic phase of the pain state, and recommend the appropriate pharmacological or non-pharmacological treatment using evidence-based

recommendations. The guidelines should also indicate when a single mode of treatment is appropriate and when multiple modes are required.[21-23]

The multimodal approach to pain management involves administering two or more analgesics with different mechanisms of action. The routes of administration may also be different. This approach is aimed at providing a synergistic effect of analgesia using the lowest possible doses of these medications than if they were used alone.[24]

Non-opioid analgesics

The following non-opioid-related medicines are available for managing pain in children: paracetamol, and nonsteroidal anti-inflammatory agents (NSAIDs), for example naproxen, ibuprofen and mefenamic acid. They adequately treat mild pain and moderate-to-severe pain in combination with other medicines, particularly opioids, to provide more effective relief and reduce adverse effects.[25]

- *Paracetamol*

Paracetamol is one of the drugs of choice in pain management, due to its excellent safety profile and lack of any significant side-effects.[26] It acts as a prodrug, with an active cannabinoid metabolite. In the brain and spinal cord, paracetamol follows deacetylation to its primary amine (p-aminophenol) which is conjugated with arachidonic acid to form *N*-arachidonolylphenolamide, a compound known as an endogenous cannabinoid. The involved enzyme is fatty acid amide hydrolase. *N*-arachidonolylphenolamide is an agonist at the Transient Receptor Potential Cation Channel, Subfamily V, Member 1 (TRPV1) receptors and an inhibitor of cellular anandamide uptake, which leads to increased levels of endogenous cannabinoids, inhibiting cyclooxygenases in the brain at concentrations that are probably not attainable with analgesic dosages of paracetamol. It is of interest to note that a cannabinoid-1 receptor antagonist, given at a dosage level that completely prevents the analgesic activity of a selective cannabinoid receptor agonist, completely inhibits the analgesic activity of paracetamol as well. This fact allows us to explain the mechanism of action of paracetamol in more detail. Despite this finding, however, the definite proof that the analgesic and antipyretic effects of paracetamol are dependent on COX-inhibition is still unclear. Hence, it works effectively when combined with codeine for more effective control of moderate-to-severe pain and discomfort.[27]

Paracetamol is available orally, in several tablet and liquid formulations, however the dosage should be guided by the age and general condition of the patient.[28]

- *Nonsteroidal anti-inflammatory drugs*

NSAIDs competitively inhibit the cyclo-oxygenase (COX) enzyme, the enzymes facilitate the bioconversion of arachidonic acid to inflammatory prostaglandins. This results in the blockade of prostaglandin synthesis and subsequently dampened inflammatory responses.[29,30] COX-1 and 2 are isozymes that only vary genetically. NSAIDs have three pharmacologically preferred attributes i.e. analgesia, anti-inflammatory and antipyretic activity. They generally have similar analgesic properties but selection is based on their receptor selectivity. COX-1 receptor activation produces gastric effects that mediate hyper-secretion of gastric acid, thinning of the lumen and propagate the development of gastric ulcers. These medicines have various formulations.[31]

The only pain medications available over-the-counter (OTC) are aspirin (S0) and paracetamol (S2) and require no prescription. The NSAID ibuprofen is S2 when intended for the treatment of post-traumatic conditions such as pain, swelling and inflammation, for a maximum period of five days without a prescription. All other NSAIDs are S3 and can only be obtained via a prescription from a physician (Act 101 of 1965).[32]

It is important to note that NSAIDs have ceiling analgesic effects but the COX-2 mediated anti-inflammatory effects are dose-dependent.[33] COX-2 is not detected in most normal tissues, but its expression is rapidly induced by stimuli such as proinflammatory cytokines (IL-1b, TNFα), lipopolysaccharides, mitogens and oncogenes (phorbol esters), fibroblast growth factor, epidermal growth factor, luteinising hormone (LH), and fluid-electrolyte haemostasis, resulting in increased synthesis of PGs in inflamed and neoplastic tissues.[29]

The NSAIDs, such as asprin, ibuprofen, diclofenac, ketorolac and mefenamic acid, have analgesic and anti-inflammatory properties, which are useful in the management of pain.[27]

Ibuprofen is one of the most frequently used NSAIDs for mild and moderate pain.[34] The medicine has gained advantage in the market as it is available as OTC medication for fever reduction, as well as pain relief. Studies have shown ibuprofen to be superior in terms of its safety profile, compared to ketorolac. However, ketorolac has been used as a single agent for the treatment of postoperative pain, especially when used as an adjuvant to opioid analgesia.[35]

If pain is constantly present, analgesics should be administered on a regular time schedule, i.e. 'by the clock', whereby the medicine is administered at a fixed time interval with dosages tailored according to the patient's pain, with the next dosage given before peak time effect of the previous dosage has worn off. This will result in more predictable and consistent levels of analgesia.[23,25]

Aspirin and paracetamol are very popular as OTC pain medication.[1] Selection of an analgesic is determined by the side-effect profile and severity of pain. Table I provides an overview of the formulations, dosages and side effects of various pain medications.

Opioid analgesics

Opioid analgesics will provide analgesia for moderate to severe pain, in the vast majority of cases and with a wide margin of safety.[36] This group includes the following examples: codeine, morphine, oxycodone, methadone, fentanyl and pethidine.

Table I: Formulations, dosages and side effects of various pain medications

Drug	Formulations	Dosages	Side effects
Paracetamol	Tablets Suppositories Intravenous solutions	1–4 g/daily 1g q 6 hourly	**Hypersensitivity skin reactions**: neutropenia, thrombocytopaenia Nephrotoxicity Hepatoxicity
Non-specific NSAIDs			
Ibuprofen	Tablets Topical patch Topical gel Oral syrup	200–400 mg q 4–6 hourly	Same as for diclofenac
Indomethacin	Capsules	25–50 mg q 6–8 hourly	**CNS effects:** Dizziness, drowsiness, mental confusion, headache in less than 10% of patients Corneal deposits
Ketaprofen	Tablets	200 mg daily with food	Same as diclofenac
Diclofenac	Tablets Intramuscular injection Topical gel Suppositories Topical patch	**Oral:** 25–50 mg q 8hourly, to maximum of 150 mg/day **Intramuscular:** 75 mg q 12 hourly, maximum of 150 mg/day for 2 days only **Suppositories:** 100 mg daily	**GIT:** Gastric erosion, peptic ulceration **Hypersensitivity reactions:** Skin rashes, pruritus and angioedema Renal toxicity
Piroxicam	Tablets Topical gel	40 mg/day	Same as diclofenac
Naproxen	Tablets	500 mg q 12 hourly	Same as diclofenac
Mefenamic acid	Oral syrups Tablets Suppositories	500 mg q 8 hourly	
COX-2 inhibitors			
Celecoxib	Tablets Capsules	100–200 mg q 12 hourly	**GIT:** Nausea, dyspepsia, diarrhoea, flatulence Steven–Johnsons syndrome **Hypersensitivity reaction:** Toxic epidermal necrolysis Renal toxicity
Etoricoxib	Tablets Capsules	60–90 mg q 12 hourly	Same as for celecoxib
Meloxicam	Tablets Capsules	7.5 mg q 12 hourly or 15 mg daily	Same as for celecoxib

Table II includes an overview of the formulations, receptors and doses of opioids. Opioids can be divided into weak and strong opioids. Weak opioids are used alone or in combination with other analgesics in the management of moderate pain. Strong opioids are usually reserved for severe pain.[3]

Opioids are the third step in the pain treatment ladder and the recommended treatment of moderate or severe pain.[37] One of the undesirable effects which is of great concern in healthcare is dependence, which is associated with prolonged use of opioids. Concomitant administration of an opioid with ibuprofen can reduce the amount of opioid analgesic required for pain control.

- *Pethidine, morphine and fentanyl*

A variety of opioids are available for use; however, there is insufficient evidence to support a preference of one opioid over another.[38,39] Pethidine does not provide good analgesia compared to morphine and should not be used long-term because of the possible accumulation of its toxic metabolite, nor-pethidine, that can result in seizures. Fentanyl provides approximately equal analgesic effects to morphine, and can be used for rapid analgesia over short periods of time if morphine is contraindicated. Opioids are the most commonly administered intravenous agents for moderate to severe pain. The opioid dosage that effectively relieves pain can differ, and should be based on a pain severity assessment. However, the long-term use of opioids is associated with constipation; therefore, a combination of a stool softener and stimulant laxative can be used as prophylaxis when it is anticipated that these agents will be used over an extended period of time.[38,39]

Morphine is well established as the first-line strong opioid and is available in both immediate-release and prolonged-release formulations. Immediate-release tablets are used to individualise patient dosages and have an adequate dosage for pain control. Prolonged-release oral formulations improve patient compliance by allowing longer dosing intervals. Oral morphine solution is usually used for persistent pain and when patients are unable to swallow tablets.[39]

The use of a pain scale to manage pain is a crucial part of effective opioid therapy because these medicines do not have a so-called

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Analgesic[2]

Skeletal Muscle Relaxant[1,2]

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100 mg Orphenadrine

FOR MILD TO MODERATE PAIN
35 mg Orphenadrine • 450 mg Paracetamol

References: 1. Norflex 100 mg tablets approved package insert, February 1985. 2. Norflex® Co Tablets approved package insert, July 1992.

Scheduling status: S2 Proprietary name (and dosage form): **NORFLEX CO Tablets**. Composition: Each tablet contains 35 mg Orphenadrine citrate and 450 mg Paracetamol. Pharmacological classification: A.2.9 (Other analgesics). Reference number: B 1098 [Act 101/1965]; Scheduling status: S2 Proprietary name (and dosage form): NORFLEX Tablets. Composition: Each tablet contains 100 mg Orphenadrine citrate. Pharmacological classification: Category: A.2.10 (Centrally active muscle relaxants). Reference number: H 1612. [Act 101/1965]. Name and business address of applicant: iNova Pharmaceuticals (Pty) Ltd. Co. Reg. No.: 1952/001640/07. 15E Riley Road, Bedfordview. Tel. No.: 011 087 0000. www.inovapharma.co.za. For full prescribing information, refer to the package insert as approved by the SAHPRA (South African Health Products Regulatory Authority). Further information is available on request from iNova Pharmaceuticals. 16849J. IN4211/21.

inova pharmaceuticals

ceiling effect. Therefore it is imperative to ensure an appropriate dosage that provides effective analgesia with manageable side-effects. A suitable opioid antagonist, such as naloxone, should also be available for the management of adverse effects or opioid-related complications.[23]

When pain management is no longer needed, slow withdrawal of opioids may be necessary to prevent abstinence syndrome, with continuous monitoring of the vital signs. This may require tapering the daily dosage whilst monitoring the level of pain, and with continuous reassessment to ensure that the patient is pain free.[39]

- *Combination opioid formulations*

When pain management with paracetamol and NSAIDs is inadequate, combination agents are usually employed. Hydrocodone and oxycodone have been increasingly used in combination with paracetamol.[37] These agents proved to be more effective in post-surgical injuries and exhibit increased pain relief compared to singular usage of NSAIDs. Caution is indicated in patients that have a previous problem with drug abuse and seizures as some patients on antidepressants (SSRIs, MOA) have experienced seizures with concomitant use of these agents.[31]

Adjuvant therapy

Adjunctive therapy is sometimes necessary to manage the side effects of medications for pain, provide symptom relief, treat anxiety and manage related or underlying conditions. This is because patients with chronic pain are more likely to report anxiety, depression neuropathic pain and significant activity limitations. Examples of adjuvant medicines include corticosteroids, anxiolytics, antidepressants, hypnotics and anti-convulsants/antiepileptic agents.[23,40]

A step-wise approach

The World Health Organization's (WHO's) 'analgesic ladder' serves as the mainstay of treatment for the relief of pain together with psychological and rehabilitative modalities. This multidimensional approach offers the greatest potential for maximising analgesia and minimising adverse effects.[23,40]

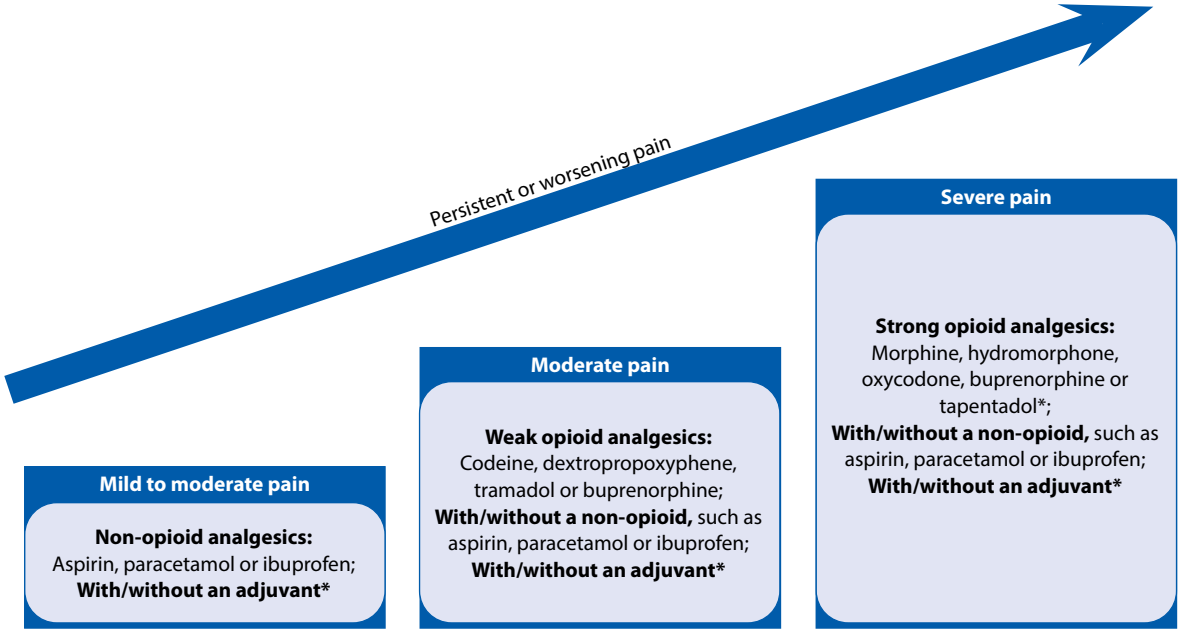
According to the WHO, the key concepts to the effective management of pain are as follows:[23,40]

- *By mouth:* If possible, analgesics should be given by mouth.
- *By the clock:* Analgesics should be given at fixed time intervals and the dosage should be titrated according to the patient's pain, and the next dosage should be given before the previous dosage has fully worn off.
- *For the individual:* The choice and dosages of the analgesics should be tailored to the needs and circumstances of the particular patient.
- *By the ladder:* The well-known WHO ladder, illustrated in Figure 2, advocates a step-wise approach to the use of analgesics, as explained below.

Step 1: Non-opioids (e.g. aspirin, paracetamol or ibuprofen) are used for mild to moderate pain.

Step 2: Weak opioids (e.g. codeine phosphate, dihydrocodeine, tramadol and buprenorphine) are recommended for moderate pain, used alone or in combination with one of the non-opioids mentioned in Step 1.

Step 3: Strong opioids (morphine, hydromorphone, oxycodone, buprenorphine and tapentadol) may be used alone or in combination with a non-opioid (from the first step) for severe pain.



[*Examples of adjuvants include corticosteroids, antidepressants, hypnotics and anticonvulsants/antiepileptic agents.]

Figure 2: The World Health Organization's three-step analgesic ladder[3]

If the patient's pain is already severe, it is recommended that the physician move to the third level of the ladder immediately, rather than starting with the first two.

As illustrated in Figure 2, opioids play an important role in the management of not only acute and chronic pain but also in the management of moderate to severe pain.[23,40]

However, certain barriers limit the effective use of opioids in the management of pain:

- Concerns about the use of opioids from healthcare workers, family members and patients; these concerns may be related to the side effects and risk of dependence when using opioids.
- Development of tolerance to the chronic use of opioids.

In instances where muscle pain does not subside with the use of mentioned analgesics, an alternative interventional therapy is muscle relaxants, where the relief of muscle spasms may also reduce pain and discomfort.[41]

Skeletal muscle relaxants are classified into two main categories namely, antispasticity and antispasmodic medications. Antispascitic medications (e.g. baclofen) act on the spinal cord or on the skeletal muscles themselves to improve muscle hypertonicity and involuntary spasms. Antispasmodic medications lessons muscle spasms through alterations of central nerve conduction. These agents are divided into benzodiazepines and nonbenzodiazepines.[41]

Anticholinergic/antihistaminic drugs

- Orphenadrine

Orphenadrine is an anticholinergic/antihistaminic drug with good central nervous system penetration and thus potent central nervous system activity. This makes it an ideal drug to treat pain of varying aetiologies.[42] Orphenadrine is derived from the antihistamine diphenhydramine through a process of monomethylation. It displays both antihistaminic and anticholinergic effects along with an independently activated analgesic effects.[43] These properties make orphenadrine both a complex and unique drug.

The analgesic properties observed with orphenadrine could potentially be attributed to its characteristic similarity to a N-methyl-D-aspartate (NMDA) receptor antagonist, whilst its anti-muscuranic properties can be attributed to its modulatory effect on the raphe-spinal serotonergic system.[44] Orphenadrine is also classified as a centrally-acting antihistamine which accounts for a portion of both its analgesic and anti-muscarinic effects.

Orphenadrine citrate is a schedule 2 drug, and is known more commonly by its trade name Norflex®. It is available in 2 ml ampoules for both IV and IM administration, however parenteral administration has increased reports of anaphylactic reactions. Oral orphenadrine citrate is available alone in 100 mg tablets, as well as in combination with aspirin and caffeine, commonly known as Norgesic® and Norgesic Forte®, respectively.[45]

Currently, the main therapeutic use of orphenadrine lies in its potential to induce analgesia and muscle-relaxation and thus it is primarily used for the management of acute painful musculoskeletal conditions.

Conclusion

Muscle pain, or myalgia, can be in one targeted area or across many muscles. The severity of muscle pain can range from mild to severe depending on the cause. It usually occurs with overuse of the muscles, inflammation or trauma causing excitation of muscle nociceptor but is also frequently associated with a viral infection. The effective management of patients with muscle pain is through a step-wise approach, offering the greatest potential for maximum analgesia and the minimum adverse effects. Non-pharmacological and pharmacological management are often applied for patients with chronic or recurrent muscle pain associated with medical disease or injury. Pharmacological management of muscle pain, depending on the severity of the pain, may include OTC medicines such as aspirin, ibuprofen and/or paracetamol; prescription medicine such as other NSAIDs (diclofenac, naproxen, mefenamic acid, etc.); or opioids for moderate to severe muscle pain. Orphenadrine can be used to treat acute painful musculoskeletal problems. Adjunctive therapy is sometimes necessary to manage the side effects of medications, provide symptom relief, treat anxiety or to manage related or underlying conditions.

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A modern approach to cough management

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Abstract

Coughing is one of the most common symptomatic reasons for patients to consult their healthcare practitioners. Their coughing may be caused by various factors such as respiratory tract infections, asthma, inhaled irritants, postnasal drip syndrome and gastro-oesophageal reflux disease. Coughing can be classified as either acute or chronic cough, and acute coughing is usually self-limiting. Patients can present with either 'wet' (chesty or productive) or 'dry' (non-productive) coughs. Unfortunately, a cough is generally uncomfortable and may interfere with daily activities, including sleep. Understanding how coughs manifest enables the health professional to provide adequate therapy. Evidence suggests that cough mixtures' effectiveness is disputable, but many patients have reported good results; hence, the medication is used in various combinations. This article provides an overview of the pathophysiology, causes and treatment of acute cough.

Keywords: cough, antitussive, mucolytic, expectorant, NTS, NAC, asthma, GORD

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Introduction

Coughing is a reflexive physiological response to external stimuli that may be intermittent or persistent. It is intended to clear the airway of secretions (mucous, oedematous fluid and pus) and particles (inhaled material, infectious agents, harmful substances and foreign particles) that accumulate within the respiratory tract. Other factors, like dysfunctional mucociliary clearance, may lead to mucus accumulation, which may require clearance by coughing.[1] Normally, a cough is purported to be protective but excessive coughing may damage the mucosa. Patients are often motivated to seek medical attention, with health professionals being requested to recommend therapies because coughing remains a common complaint.[2,3]

Pathophysiology

Coughing results from repeated stimulation of a complex cough reflex arc that originates from afferent impulses from sensory nerve fibres that lead to the cough centre located in the upper brain stem and pons and then back to the diaphragm, abdominal wall and inspiratory and expiratory muscles via the efferent pathway.[3,4] This is initiated by particulates irritating the countless cough receptors that are located mainly in the trachea, bronchi and larynx, but also in the external auditory canals, eardrums, paranasal sinuses, pharynx, diaphragm, pleura, pericardium and stomach.[3,4] These receptors are sensitive to either physical or chemical stimuli, such as heat, acid and capsaicin-related compounds.[4] These receptors include rapidly-adapting receptors (RAR), slow-adapting stretch receptors (SARs) and C-fibres. A stimulatory signal is conveyed by an afferent pathway using the vagus nerve to the solitary tract nucleus or nucleus tractus solitarius (NTS) located in the medulla oblongata. The central coordinating region for coughing is located in the upper brain stem and pons.[5] In response to stimuli, the medulla sends a signal via the efferent pathway in the vagus, phrenic, and spinal motor nerves to expiratory musculature, mainly the diaphragm, laryngeal and bronchial muscles, to produce the cough.[4] Once a stimulus has triggered the cough reflex, the following phases become activated sequentially:

- **Inspiratory phase:** The chest cavity expands and allows for air to flow inwards, resulting in the expansion and filling of the lungs, with a resultant increase in pressure, to a volume necessary for an effective cough to be produced.
- **Compression phase:** The larynx will close, and the respiratory muscles start contractile movements to further increase pulmonary pressure in anticipation of the expulsion event.
- **Expiratory phase:** Opening of the larynx, coupled with further contractions of the respiratory muscles, forcing out air at high velocity.[4,6]

Refer to Figure 1 for an illustration of the cough reflex.

Aetiology

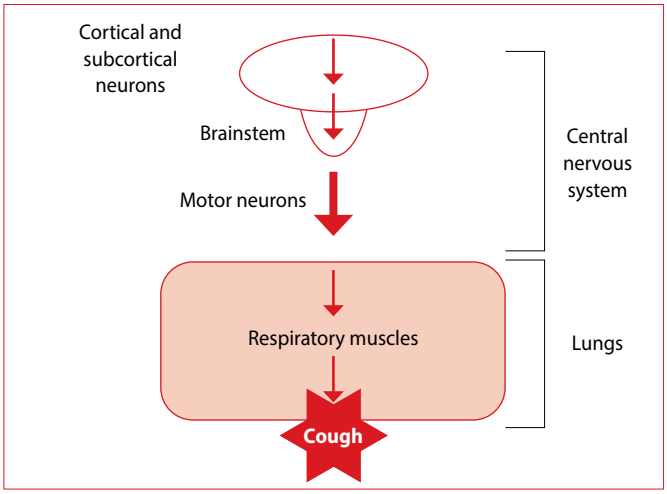

Figure 1: Simplified cough reflex pathway[7]

Coughing can be classified as either acute or chronic. An acute cough is a daily cough that lasts for fewer than three weeks, whilst a chronic persistent cough typically lasts more than eight weeks.[3,8] Coughing that lasts between 3–8 weeks (usually a product of bronchial sensitivity and hyper-responsiveness or post-infection) is referred to as subacute coughing.[3,6] Subacute coughs may precipitate an infection if not adequately resolved. Unfortunately, there is inadequate data to determine accurate and directed therapy, hence in practice, inhaled corticosteroids and leukotriene modifiers have been used. However, literature signifies that once the hyper-responsive phase has passed, coughs become self-limiting.[9] Chronic coughing lasts for three months or more, but not more than two years. Possible causes may be cancerous, an effect of the smoking habit, gastro-oesophageal reflux disease (GORD), asthma and certain medicines.[10]

There are various types of coughs depending on the origin and pathway of stimulation, which may be used to determine the diagnosis and tailor the treatment of the condition. A pharyngeal cough is usually dry and not particularly strong (i.e. a so-called dry cough). A dry cough does not produce any mucus and is often painful. A pharyngeal cough occurs in convulsive attacks with loud inspirational sounds likened to whooping. A cough that originates from the larynx is usually associated with hoarseness of the voice.[10] Restrained coughing occurs in children with dyspnoea or pleural pain and is often identifiable by the child's distinct effort to suppress the cough reflex. A dry cough is a distinctive sign of upper respiratory involvement.[11]

Conversely, a productive or so-called wet cough signifies the likely involvement of lower respiratory tract disease.[12] It is mainly characterised by its exudative nature, whereby phlegm is produced. Phlegm is a type of mucus produced in the lower respiratory tract. In some instances, the colour and texture may determine the nature of the pathology. The presence of blood in the phlegm or sputum may represent physical damage to the mucosal lining. Refer to Table I for a comparison of the causes of wet (productive) versus dry (non-productive) cough.

Table I: Causes of productive versus non-productive cough[7]

Productive (wet) cough	Non-productive (dry) cough
Chronic bronchitis	Postnasal drip
Air pollutants/irritants	Viral infection (common cold)
Allergic conditions, including asthma	Gastro-oesophageal reflux disease (GORD)
Aspiration	Medication-induced coughing (e.g. ACE-inhibitors)
Lung cancer	Heart failure
Pneumonia or tuberculosis	Psychological causes

Diagnosis

A physical examination of the patient should focus on history and signs of possible sinusitis, postnasal drip and rhinitis. The physician must perform chest auscultations during a cough to assist with the diagnosis of various disease states. In the absence of a clear aetiology, the physician must order a chest X-ray.[10] This test provides a static, structural image of the lungs to demonstrate abnormalities (e.g. over-secretion of mucus or inflammation of the mucosal lining). The elimination of possible differential diagnoses is significant in directing the best possible treatment plan. In the case of asthma, the patient's history of symptoms coupled with spirometry is used to confirm the diagnosis. When GORD is the underlying pathology, an oesophageal pH test must be performed.[10]

Treatment

It is paramount that the underlying condition is correctly managed because a cough tends to be a symptom of underlying pathology rather than a disease condition. The use of mucolytics, expectorants, antitussives, bronchodilators and antihistamines are used to manage a cough.[10] A cough is designed to expel irritants from the airways.[13]

Antitussives

Dextromethorphan, codeine and hydrocodone are used to suppress the cough by decreasing the excitability of afferent nerves that stimulate the cough reflex (i.e. menthol), whereas some directly inhibit the medullary cough centre.[13] Menthol is classified as a locally-acting antitussive and may be administered as a throat spray or lozenge. Opioid agonist antitussives are centrally-acting, meaning that they directly inhibit the cough centre in the medulla oblongata, but they are better as analgesics and produce a euphoric effect,[13] hence their routine use has become increasingly undesirable. Dextromethorphan is an isomer of a very potent opioid, but at lower dosages it does not produce analgesia, euphoria or drowsiness. Codeine (10–20 mg every 4 to 6 hours) and hydrocodone are available in tablet and syrup form. Unfortunately for the patient, suppressing a wet infectious cough is not recommended because the sputum, usually comprised of bacterial debris and pus, may precipitate therapeutic failure when not effectively cleared from the lower airway.[10]

Pholcodine is comparable to dextromethorphan in terms of its efficacy in the management of patients with acute dry (non-productive) coughing. Similarly to the other antitussives, this agent can reduce the patient's mean daytime cough frequency, mean nighttime coughing, and the intensity of the cough itself.[14]

Expectorants

Guaifenesin can assist with the expulsion of mucus and particulates from the lungs. It is postulated that this agent reduces adhesiveness and surface tension of secretion found in the respiratory tract.[12] Although an antitussive, guaifenesin (200–400 mg orally every 4 hours) reduces the occurrence of coughs and is reserved for viscous secretions in patients with a dry, non-productive cough.[15] Hydration of the airway is required to improve therapeutic outcomes.[11] Other expectorants include bromhexine and ipecac.[8]

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There are significant differences between physiological and pathological mucus in the airways. Airway pathology results in the creation of a more viscous sputum that is significantly more difficult for the patient to expel from the lungs.[16] Bromhexine has been clearly shown to reduce mucus viscosity, thereby assisting the patient with sputum expectoration.[16,17] In a more recent reappraisal of bromhexine, published in 2017, the authors even showed that bromhexine augmented certain antibiotics' actions when the latter was co-administered with this particular expectorant. This resulted in a more favourable clinical response to antibiotic treatment.[16] Bromhexine was found to be well tolerated with a favourable safety profile.[16]

Mucolytics

These agents are intended to reduce the surface tension and mucus viscosity of the lower airway secretions. N-acetyl cysteine (NAC) also possesses antioxidant properties and is classified as a classic mucolytic. NAC depolymerises the mucin glycoprotein oligomers by hydrolysing the disulphide bonds that link the mucin monomers through free thiol (sulfhydryl) groups.[15] Mucin is a polyionic tangled formation with charged side chains that ensure the structure is maintained. They hydrolyse disulphide bonds reducing mucus viscosity.[18] Literature has not provided evidence that NAC provides beneficial effects in the expulsion of mucus. Oral NAC is rapidly broken down and is not present in mucus. Peptide mucolytics depolymerise the DNA-polymer (i.e. dornase alfa) or the F-actin network and are most effective when sputum is rich in DNA pus.[15]

Antihistamines

First-generation antihistamines include diphenhydramine, promethazine, phenyltoloxamine (tablet) and triprolidine. These antihistamines act as a cough suppressant by reducing cholinergic transmission of nerve impulses in the coughing reflex. Non-sedative antihistamines lack cholinergic effects and hence are less effective for cough therapy.[8] Antihistamines have been used in congestion and postnasal drip to reduce the frequency of coughing. These agents are most effective in allergic conditions.[19] The combination of an antihistamine and a cough suppressant can be used for nighttime coughing. Antihistamines suppress coughing, but combined use with an expectorant that promotes coughing would not be therapeutically plausible.[8] Table III briefly summarises the treatment indications of the main groups of medication used to manage wet and dry cough.

Bronchodilators

There is a scarcity of data supporting enhanced mucociliary clearance due to bronchodilators but they increase cough clearance by increasing expiratory flow.[15] Agents such as terbutaline have a more pronounced enhancement of mucociliary function. The effect of bronchodilators is more pronounced in asthma-related coughs whereby salbutamol and theophylline are used.[6] Other agents, including β_2-adrenoceptor agonists, muscarinic receptor antagonists, and xanthines, are sometimes used in combination. Theophylline has a narrow therapeutic index which may lead to toxicity in vulnerable populations.[18]

In addition to its adrenergic effects, salbutamol has, however, also been shown to inhibit the release of bronchoconstrictive agents from mast cells in the lower airway, reducing the severity of bronchial oedema. In addition, some evidence does suggest its positive effect on mucociliary clearance, making it a useful active ingredient in a suitable cough mixture. Furthermore, salbutamol makes for an excellent active ingredient, in combination with bromhexine, for a so-called tight chest.[17]

Cough mixture stability

Cough syrups are pharmaceutical solutions that are susceptible to chemical degradation reactions (e.g. hydrolysis, oxidation,

Table II: Drugs used in the management of cough[9,16,18]

Pharmacological group	Pharmacological active ingredients	Mode of action	Indication	Side effects
Antitussives	Codeine	Suppresses cough reflex by suppressing the cough centre in the medulla	Non-productive cough	Sedation, constipation, nausea, dizziness, respiratory depression, confusion
	Dextromethorphan	Centrally-acting N-methyl-D-aspartate (NMDA) receptor antagonist; directly suppresses medullary cough centre		
	Pholcodine	Centrally-acting opioid derivative, directly suppressing medullary cough centre		
Expectorants	Guaifenesin, Bromhexine	Stimulates secretions and reduces mucus viscosity Reduces bronchial sputum surface tension	Cough alleviation of a non-productive cough with viscous mucus	Drowsiness, dizziness, headache, nausea, diarrhoea, rash
Mucolytics	N-acetyl cysteine	Depolymerises the mucin glycoprotein oligomers by hydrolysing the disulphide bonds in mucoproteins to reduce the viscosity of secretions	Respiratory conditions with viscous mucus	Nausea, vomiting, bronchospasm, headache, fever, urticaria, skin rashes, abdominal pain, diarrhoea

reduction, decarboxylation and epimerisation) due to chemical incompatibility, photodegradation reactions and changes in pH. Stability should be maintained throughout the products' shelf life. This can be achieved by controlling the pH, moisture content and storage conditions (temperature, light and humidity) of the product.[20] The packaging materials used in the container closure system are also critical for product stability. Glass and aluminium packaging is more resistant to oxidation, heat, sorption and permeability than plastic packaging material.[21] Amber or opaque containers help prevent photooxidation.[21]

Cough mixture combinations and compounding in South Africa

Cough mixtures contain both pharmacologically active compounds and various excipients, which cannot be regarded as simply inert.[21,22] There are various cough mixture combinations available on the South African market (Table III).[18] Apart from the commercially available cough mixture combinations, healthcare providers often compound their own combinations of syrups that may include antihistamines, bronchodilators, mucolytic, corticosteroids and herbal cough syrups without their having any stability data on the compounded combination. Degradation due to chemical incompatibility occurs between formulation ingredients that react with one another. Therefore, it is imperative to do thorough research on the various stability factors that should be considered before compounding just any cough mixture.[21,23]

Official monographs can be consulted for information on active ingredients, whilst the Handbook of Pharmaceutical Excipients contains monographs with comprehensive information on the safety, handling and physical and chemical properties of excipients.[22,24] The Association of Compounding Pharmacists of South Africa (ACPSA) may also be able to provide direction on combining cough syrups.

Table III: Cough mixture combinations[18]

Antihistamine + decongestant + cough suppressant
Antihistamine + expectorant + bronchodilator
Antihistamine + decongestant + expectorant + cough suppressant
Antihistamine + expectorant
Bronchodilator + expectorant
Bronchodilator + mucolytic

Conclusion

Apart from a more serious aetiology such as the prevalent SARS-Cov-2, an acute cough is usually self-limiting and is mostly a result of either a common cold or an allergic condition. Treatment of a cough must be directed at symptomatic relief. Sensitisation of the cough reflex is a common feature in these patients, irrespective of the underlying cause. Although a large variety of cough preparations are available and commonly used, evidence for the efficacy of some of their active ingredients remains limited.

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Acne and its management – an update

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Abstract

Acne vulgaris is quite common during adolescence but also occurs in children, adults, and pregnant women. It is a condition in which androgens are produced during puberty and induce hypertrophy of the sebaceous glands, and the excess secretory rate in predisposed individuals triggers acne. Sebum promotes the growth of a resident anaerobic bacterium on the skin, *Propionibacterium acnes* (*P. acnes*) also known as *Cutibacterium acnes (C. acnes)*. Acne affects areas of the skin with large numbers of sebaceous glands. Treatment of acne can be done topically with retinoids, azelaic acid, benzoyl peroxide or topical antibacterials or systemically with oral antibacterials, hormonal therapies or isotretinoin. The pharmacist plays a particularly important role in educating patients about correct skin care products and medications used to treat acne, especially in women of childbearing age. This article is an update of the 2020 version and includes new insights regarding acne vulgaris.

Keywords: acne, acne vulgaris, azelaic acid, benzoyl peroxide, clindamycin, contraceptives, *Cutibacterium acnes (C. acnes)*, erythromycin, isotretinoin, *Propionibacterium acnes (P. acnes),* spironolactone, retinoids, teratogenicity, tetracycline, updates of acne vulgaris management

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Introduction

A literature review was undertaken using PubMed, Science Direct and internet sources to compile this article. Keywords such as "acne", "management of acne", "causes of acne", "*P. acnes*", "isotretinoin"; "benzyl peroxide", "retinoids", "azelaic acid", "*Propionibacterium acnes*","*Cutibacterium acnes*","*C. acne*","updates of management of acne" and "acne vulgaris" were used as well as other articles selected and studied.

The role of the pharmacist in the management of acne cannot be underestimated. The pharmacist's role commences when a prescription is received and needs to be dispensed. It also results in the supplying of advice to the patient as to when the medication(s) need to be taken, how they need to be taken, which side effects can be expected and when a referral is needed.

Acne is very common in adolescence and while it regresses in the late teens or early twenties, half of those affected continue to experience symptoms into adult life. Acne affects 80% of people at some point between 11 and 30 years of age. During adolescence, acne is more common in male than in female patients.[1] Acne affects areas of the skin with large numbers of sebaceous glands, especially in the face, neck, back and chest. The pathogenesis of acne vulgaris is multifactorial, such as genetics, increased sebum production, (particularly in response to androgens), *P. acnes* proliferation and inflammation.[2] High-resolution core genome studies have reported a new genus called *Cutibacterium* gen. nov. As a result of the 16S rRNA gene sequences, DNA G + C content, genome size, and gene content, *P. acnes* was renamed as *Cutibacterium acnes* (*C. acnes*).[3]

On the skin surface, the microbial community is mostly constituted by bacteria belonging to the three main genera of *Corynebacteria*, *Propionibacteria* and *Staphylococci*. The interplay between these cutaneous microbiota is essential for the maintenance of a healthy skin. Although *Cutibacterium acnes* (*C. acnes*) is predominantly present in sebaceous sites, it also plays a critical role in the regulation of skin homeostasis and prevents colonisation from other harmful pathogens.[4] It is further stated that it can also act as an opportunistic pathogen in acne vulgaris.

New findings on *C. acnes* reveal that its proliferation is not the trigger of acne but instead it maintains tight equilibrium between members of the skin flora and among *C. acnes* phylotypes, which may play a critical role in acne onset.[4] Colonisation of the pilosebaceous follicle by *C. acnes* is considered one of the critical factors driving acne by initiating the inflammatory response of the skin, in addition to the cutaneous microbiota and innate immunity. Two other factors involved in this chronic inflammatory skin disease are (i) the increased sebum production and hypercornification of the pilosebaceous follicle (which results due to hyperproliferation) and (ii) abnormal keratinocyte differentiation of the upper part of the follicle.[5] There are many other contributing factors which influence the severity, incidence and persistence of acne, e.g., environmental factors, hormones, family history and stress.[7]

A small number of other causes have been implicated in the pathogenesis of acne. These include cosmetic agents and hair pomades, medications (corticosteroids, lithium, iodides), hyperandrogenism and mechanical occlusion with headbands, shoulder pads and backpacks.[1] In women, acne can be a manifestation of polycystic ovarian syndrome, while smoking and a diet rich in dairy products or with a high glycaemic load, increase the risk for the development of acne.[7]

Sex hormones and metabolic hormones seem to play a role in the development and severity of acne. For example, elevated dehydroepiandrosterone (DHEAS), dihydrotestosterone (DHT), and insulin-like growth factor 1 (IGF-1) positively correlate with

increasing acne lesion counts in women and androstenedione and DHEAS in men.[8]

The various hormones possibly implicated in acne and their proposed mechanisms are summarised below.[9]

- *Androgens* (testosterone, DHT, DHEAS) increase the size and secretion of sebaceous glands. Sources of circulating androgens include the adrenal glands, ovaries, or testes. Androgens can also be produced locally within the sebaceous gland; for example, testosterone can be converted to DHT by the type 1, 5-α-reductase of the sebaceous gland.
- *Oestrogens* counter the action of androgens by three potential mechanisms: direct opposition locally, inhibition of androgen production in the gonads via feedback loop, or gene regulation.
- *Growth hormone* and *growth factors* – growth hormone stimulates the production of growth factors such as IGF-1, both of which are secreted in high levels during puberty when acne is at its peak incidence. In some tissues, possibly including sebaceous glands, the action of IGF-1 is influenced by androgens.
- *Melanocortins* (melanocyte-stimulating hormone, adrenocorticotrophic hormone [ACTH]) regulate sebum production.
- Other unknown mechanisms.

Androgens are produced during puberty and induce hypertrophy of the sebaceous glands and the excess secretory rate in predisposed individuals triggers acne; however, acne can also be triggered using anabolic steroids.

Increased sebum production in response to androgenic stimulation distends the pilosebaceous glands. Proliferation of keratinocytes causes hyperkeratosis at the mount of the follicle, which blocks the duct and produces a small, closed papule (comedo) called a whitehead. If this duct opens, compacted follicular cells and oxidised melanin at the tip give comedones the appearance of a blackhead.[10,11]

Sebum promotes the growth of a resident anaerobic bacterium on the skin, *C. acnes*, which degrades triglycerides in sebum to free fatty acids and glycerol. *C. acnes* also release chemotactic factors and inflammatory mediators, which trigger an inflammatory response by activation of toll-like receptors and the induction of pro-inflammatory cytokines.[12] The combination of released mediators with the irritant-free fatty acids produces inflammatory lesions (papules, pustules, and nodules),[10,11] which coalesce to form multilocular cysts. These inflammatory lesions can scar, leaving permanent disfigurement. The pathophysiology of acne vulgaris can be seen in Figure 1. Release of elastase by activated neutrophils causes connective tissue damage and scarring. Post inflammatory hyperpigmentation is common in dark-skinned patients.

Mild acne is confined to the face and consists of papules and pustules with few inflammatory lesions. Moderate acne usually also involves the trunk and has increased numbers of inflammatory lesions, while severe acne presents with nodules and cysts, which are widespread.[10]

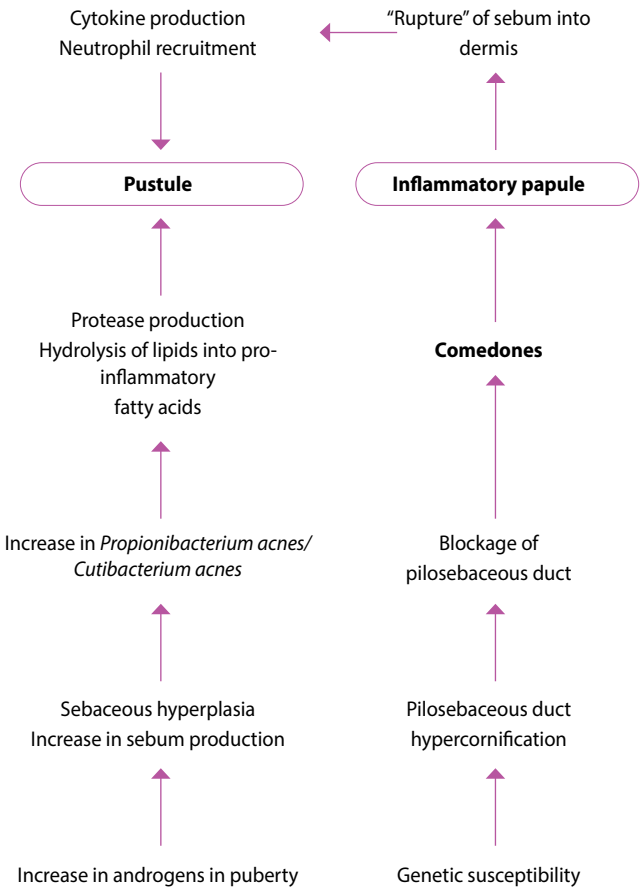

Figure 1: Pathophysiology of acne vulgaris[12]

Diagnosis is straightforward, and most patients will generally seek appropriate advice on correct product selection.

Acne exposome is defined as the sum of all environmental factors influencing the occurrence, duration, and severity of acne. Exposome factors impact the response and the frequency of relapse to treatments by interacting with the skin barrier, sebaceous gland, innate immunity, and cutaneous microbiota. They may be classified into the following six main categories: nutrition, psychological and lifestyle factors, occupational factors including cosmetics, as well as pollutants, medication, and climatic factors.[13]

Nutrition

This first category is by far the most published acne exposome factor. Main food classes considered to trigger acne are dairy products (especially skim milk) and hyperglycaemic carbohydrates. An average regimen of dairy products has been reported impacting on acne, and one paper indicated that cow milk impacts acne after drinking two glasses per day.[14,15]

Medication

The following androgenic progestins have been identified to cause or worsen acne: desogestrel and 3-cetodesogestrel, levonorgestrel, lynestrenol, norgestrienone, norethisterone, norgestrel, gestodene, norgestimate and etonogestrel. In contrast to this, chlormadinone acetate, dienogest, drospirenone and

norgestimate oral contraceptive pills have been reported to be beneficial in the treatment of acne. Corticosteroids, halogens, isoniazid, lithium, vitamin B_{12}, immunosuppressants and certain anticancer agents and radiotherapy have been reported as causing acneiform eruptions.

Occupational factors, e.g. cosmetics; mechanical factors

The use of aggressive skin care regimens and inappropriate cosmetics may cause acne flare-ups. These products modify the skin barrier and the skin microbiota balance, especially in the sebaceous area, thus activating the innate immunity and triggering inflammation.[13]

Mechanical factors comprising rubbing, scrubbing, the use of home devices or medical devices such as sonic brushes, derma rollers or microneedling systems may trigger acne flare-ups.[16]

Pollutants, e.g. air, industrial and human-dependent pollutants

Air pollutants exert a harmful effect on the skin by increasing oxidative stress inducing severe alterations of the normal functions of lipids, deoxyribonucleic acid and/or proteins in the human skin.[17]

Acne has been frequently observed in industrial workers after prolonged exposure to specific organic molecules, such as coal, tar, or crude oil.

Tobacco and cannabis use may be considered human-dependent pollutants, which may play a role in acne.

Climatic conditions

Climatic conditions and seasonal variations resulting in a combination of heat, humidity and intensive ultraviolet rays (UVR) may trigger inflammatory acne flare-ups, which have been called acne tropicana, acne majorca or tropical acne.[18]

One of the major environmental factors affecting the skin is ultraviolet radiation. Both UVB and UVA have been reported to cause hyperplasia of the sebaceous gland, thickening of the stratum corneum, increase in sebum secretion and the number of comedones.[19]

Psychosocial and lifestyle factors

Modern lifestyle, defined as stressful situations including urban noises, socioeconomic pressures, and light exposure, may play a role in acne.[13]

Although acne is often considered a cosmetic problem, the condition can have a significant impact on patients' psychosocial and physical well-being. It may have a lifelong effect from disfiguring scars. The presence of acne correlates with various psychological factors such as depression, anxiety, anger, frustration, shame, low self-esteem, social isolation, and body dissatisfaction.

Patients with acne have been shown to have an increased risk of depression and suicide attempts, even when under treatment for depression. Among those with severe acne, the risk of suicidal ideation may be two to three times that of their unaffected peers. Behavioural signs such as poor eye contact, angry or negative verbalisation, poor self-care and personal hygiene, compulsive behaviours, or self-mutilating behaviours may also be considered high risk. Patients with acne should be assessed for suicidal tendencies and depression, and anyone with a concerning diagnosis should be appropriately referred.

Clinical features

Acne occurs in the face and upper trunk, where the sebaceous glands are very dense and the affected areas are greasy.

The stages in the development of acne include the following:[20]

- Whiteheads
- Blackheads
- Papules
- Pustules
- Cystic acne

Whiteheads (closed comedones) are seen when sebum in the follicle increases, leading to a dilatation in the opening of the sebaceous duct. Blackheads (open comedones) have a similar development as a whitehead but differ from them in that the opening of the dilated follicle is blocked by a mass of keratin. The black colour is not due to dirt but due to the melanin in the keratin plug.

Papules develop from a whitehead. Two types are seen, namely: a non-inflammatory type, lasting for about two weeks and an inflammatory type. The inflamed papule is characterised by being slightly uncomfortable, and the area of the skin is tender. Close examination reveals a slight inflammation in and around the lesion. These lesions may develop in pustules or resolve spontaneously over a period of two to three weeks.

Pustules develop when the epidermis is destroyed and an abscess forms within the follicle.

Cystic acne occurs when the contents of the comedone spread into the surrounding tissue and into adjuvant follicles and may reach several centimetres in diameter. When aspirated with a large bore needle, viscous, creamy yellow material is drained. Cysts may be widespread and affect the face, back, chest, neck, and scalp.

Patients suffering from mild acne predominantly have open and closed comedones, white and blackheads, with a small number of active lesions usually confined to the face. The degree of severity needs to be assessed and if necessary, refer the patient to a medical practitioner. Generally, if there are widespread facial lesions as well as chest and back involvement, referral is advised. Referral is also indicated when there is moderate or severe acne, occupational acne, over-the-counter (OTC) treatment failure and rosacea.[21]

Table I gives the Global Acne Grading System (GAGS), from which a global score can be calculated indicative of the severity of acne.

Another source provides a GAGS calculator in which another means of classification can be calculated.[22]

Table II gives a South African grading severity classification and applicable treatment.

Management of acne

Non-pharmacological management

Non-pharmacological therapies are applied more often by healthcare professionals such as pharmacists, general practitioners and dermatologists. The most applied non-pharmacological therapies include laser and light-based therapies, chemical peels, microneedling, (micro) derma abrasion and (mechanical) lesion removal. Non-pharmacological therapies are applied as independent therapies, in combination with conventional therapies or as maintenance therapy, especially in more persistent or chronic types of acne where long-term therapy is required.[25,26]

Light and laser treatments are relatively new non-invasive therapies for acne. Light and laser therapies (photodynamic therapy, blue light, intense pulsed light) are commercially available, particularly in the private sector.[1] Intralesional corticosteroid injections, usually triamcinolone acetamide diluted to 5 mg/ml or less, can be used to flatten nodules or cysts within 48 to 72 hours.[1]

Some references regarding the antibacterial effects of natural products are cited below.

It was found that plant extracts may be an alternative treatment for acne. Weber et al. reported that hop extract has a high antimicrobial activity against *P. acnes* (minimum inhibitory concentration [MIC] of 3.1 µg/ml).[27]

Herbal ball extract with Kalmegh, rosmarinic acid, *Centella asiatica* extract, and *Rosa damascena* methanolic extract also exhibited antimicrobial activity against *P. acnes*.[28]

Boswellia serrata extract is effective at low concentrations against *P. acnes* (MIC of 1 µg/mL).[29]

Only a limited number of studies have indicated the anti-*P. acnes* activities of herbal tea extracts. DuZhong extract showed the highest level, yerba mate extract showed a moderate level, and rose extract showed the least.[30]

Table I: Global Acne Grading System (GAGS)[23]

Location (L)	Clinical assessment (A)	Local score	Global score
Forehead = 2	0 = no lesion	Local score = L times (x) A	0 = none
Right cheek = 2	1 = ≥ 1 comedon		1–18 = mild acne
Left cheek = 2	2 = ≥ 1 papule		19–30 = moderate acne
Nose = 1	3 = ≥ 1 pustule		31–38 = severe acne
Chin = 1	4 = ≥ 1 nodule		> 39 = very severe acne
Chest/upper back = 3			

Table II: South African grading severity,[24] symptoms and medication of choice

Grade	Symptoms/presentation	Medication of choice
Grade 1 (mild)	Comedones only	Topical retinoids (adapalene, tretinoin or isotretinoin **Alternatives:** Topical benzoyl peroxide, topical azelaic acid, comedo extraction for persistent, large comedones
Grade 2 (moderate)	Comedones + red papules	Topical retinoids plus antimicrobial preparations: - For superficial papules: Topical adapalene/benzoyl peroxide (BPO) combination product **Alternatives:** Topical retinoid at night, topical benzoyl peroxide in the morning; topical retinoid at night plus clindamycin/benzoyl peroxide combination product in the morning
Grade 3 (moderate severe)	Comedones + red papules + pustules	Method of choice: Topical retinoids plus oral cyclines **Alternatives:** Topical retinoids plus combined oral contraceptives containing cyproterone acetate for women Topical retinoids plus dapsone
Grade 4 (severe)	Comedones + red papules + pustules + nodules/cysts/conglobate lesions	Method of choice: Oral isotretinoin (OIT) as a full course **Alternatives:** Topical retinoids plus combined oral contraceptives containing cyproterone acetate, with added cyproterone acetate as 10 mg per day on days 5–19 of the menstrual cycle Topical retinoids plus dapsone 100 mg per day
Acne fulminans	The above + ulceration + fever and other synthetic symptoms	–

Furthermore, it is also noteworthy to mention that other (new) advances in the treatment of acne that *may* emerge as targets for future acne treatments include: (i) the cutaneous loss of diversity of *C. acnes* phylotypes. The loss of diversity of microbiota in acne provides the rationale for the potential use of oral/topical probiotics. Another therapeutic approach is to modulate the microbiota in the topical formulation of *C. acnes* bacteriophages to target specifically the pathogenic 'acnegenic' *C. acnes* phylotypes and (ii) to target the insulin-like growth factor-1 signalling pathway. Insulin-sensitising agents such as metformin, myo-inositol and D-chiro-inositol represent promising agents, but to date there have been only limited studies and much heterogeneity in the methods of assessing acne efficacy outcomes.[31]

Pharmacological management

The main groups of therapeutic medicines are topical and systemic retinoids, antimicrobial agents, and systemic hormonal medicines. Antibiotics that are used include the following: clindamycin, tetracyclines, erythromycin, metronidazole, nadifloxacin, and dapsone which are used for anti-*C. acnes* therapy. Long-term antibiotics usage is controversial because of the development of bacterial resistance. Currently, new retinoids are being used in combination with antibiotics to decrease the risk of bacterial resistance.[2]

Acne should be treated actively to avoid unnecessary scaring and psychological distress. There are several effective anti-acne treatments on the market, with the choice of therapy dependent on the nature of the lesions and their severity.

Topical treatments

The ideal topical treatment combines a keratolytic preparation and a topical antibacterial agent. Removal of the top layer of the skin leads to exposure of the follicle to become more aerobic (oxygenated), thus creating an environment that is no longer ideal for bacterial multiplication, especially *C. acnes*. Also, when the top layer of the skin is removed, the topical antibiotic can now penetrate the follicle and kill the bacteria involved.[20]

- *Retinoids* (e.g., isotretinoin and adapalene) are vitamin A derivatives with a keratolytic action that unblocks the pilosebaceous follicles and allows the flow of sebum to extrude the plug (comedolytic action). Topical retinoids can cause erythema and scaling, which can be minimised by starting on a low concentration. These preparations are used in a cream or gel formulation at concentrations of 0.025–2.5%. These preparations should be applied alone. Adapalene is an extensively modified retinoid and has a faster onset of action compared to that of isotretinoin, and it produces less skin irritation.[18]
- *Azelaic acid* has antibacterial action against *C. acnes* and is effective against bacteria that have become resistant to erythromycin and tetracycline. It also inhibits keratinocyte division, which may reduce follicular plugging and prevent comedone development. The most frequent side effects include local burning, scaling, or itching, while hypopigmentation can become problematic in darker skin tones.
- *Benzoyl peroxide* has antibacterial activity against *C. acnes* by generating reactive oxygen species in the follicle and also exhibits weak anti-inflammatory and keratolytic actions. It can be fast-acting, with a response rate as early as five days.[32] It is responsive when there are inflammatory lesions present. Benzoyl peroxide produces scaling and skin irritation, especially in high concentrations, although this may be transient. It can bleach clothing and hair and degrades isotretinoin (but not adapalene) and should be applied separately. Owing to its potential to cause erythema and irritation, concentrations of 10% should be avoided, since 5% and 10% concentrations seem to be equally efficacious.[21] Benzoyl peroxide prevents the resistance of *C. acnes* to antibiotic therapy and has moderate comedolytic and anti-inflammatory properties.
- *Topical antibacterials* (e.g. clindamycin and erythromycin) are less effective compared to oral antibacterials but have fewer side effects. They possess weak anti-inflammatory and comedolytic action in addition to their direct action against *C. acnes*. Since bacterial resistance develops with regular use, they should be applied together with either benzoyl peroxide or a topical retinoid to improve antibacterial penetration into lesions, as well as for their synergistic actions on the lesions. Topical antibacterials should not be used for more than 12 weeks.

Systemic treatments

Propionibacterium species are intrinsically resistant to metronidazole, tinidazole and ornidazole, aminoglycosides, sulfonamides, and mupirocin, while *C. acnes* is susceptible to many antimicrobials. However, studies have reported that *C. acnes* has high rates of resistance to erythromycin and clindamycin.[33,34]

Bacterial biofilms also play an important role in antibiotic resistance and decrease the susceptibility to antibiotherapy.[35] The ability of biofilm formation of *C. acnes* was reported in 2007.[36] Studies have indicated that the development of *C. acnes* biofilms was higher in patients with acne than in normal patients.[37]

- *Oral antibacterials* (especially lymecycline and doxycycline) have antibacterial action against *C. acnes* as well as anti-inflammatory action and are prescribed for inflammatory acne (papules/pustules). Treatment should be given for no longer than 12 weeks and should be combined with a topical retinoid or benzyl peroxide to improve efficacy. Ciprofloxacin and trimethoprim can also be used, but their use is limited due to widespread tetracycline and erythromycin resistance. Oral antibiotics should not be prescribed for non-inflammatory acne and should be used in conjunction with a non-antibiotic topical agent, as this improves effectiveness and reduces bacterial resistance. Other

antibiotics used include tetracycline and oxytetracycline. Table III lists oral antibiotic therapy for acne vulgaris.

Table III: Oral antibiotic therapy used for acne vulgaris[38]

Antibiotic, dose	Notes
Tetracycline, 250–500 mg twice daily	• Inexpensive • Contraindicated in pregnant women and children under nine years of age • Chelated by antacids and milk • To be taken on an empty stomach
Minocycline, 50–200 mg daily	• Can be taken with food • Contraindicated in pregnant women or children under one year of age • Adverse effects: dizziness; pigment changes; hepatitis; lupus-like reactions
Doxycycline, 100–200 mg daily	• Can be taken with food • Acceptable for use in patients with renal failure • Contraindicated in pregnant women or children under nine years of age • Adverse reactions: gastrointestinal upset; photosensitivity (greatest of all tetracyclines)
Erythromycin, 500 mg twice daily	• Safe for pregnant women and children • Adverse effect: may cause gastrointestinal upset • 42% may show resistance to *C. acnes*
Trimethoprim/ sulfamethoxazole 80/40 mg or 160/80 mg, four times per day	• Useful in patients resistant to other antibiotics • Adverse reactions: 3–4% of patients experience a rash; risk of serious skin reactions, such as Steven–Johnson syndrome

Table IV gives the main pathogenic factors in acne and their corresponding treatments.

Table IV: Main pathogenic factors in acne and corresponding treatments[24]

Pathogenic factor	Relevant medication
Androgen stimulation of sebaceous glands	Cyproterone acetate, drospirenone
Hypersecretion of sebum	Oral isotretinoin
Hyperkeratosis and occlusion of the duct that drains sebum into the hair follicle	Topical retinoids
The formation of the invisible microcomedo	Topical retinoids
Inflammatory mediators (Interleukin 1 etc.) released after stimulation of the toll-like receptor 2 by *C. acnes*	Topical retinoids and isotretinoin
Neutrophilic response to rupture of comedones and inflammation induced by free fatty acids in sebum	Oral cyclines, oral and topical dapsone, oral macrolides
Proliferation of *C. acnes*	Oral cyclines, oral macrolides, topical benzoyl peroxide
Inflammatory tissue damage by matrix metalloproteinases	Oral cyclines

The following illustrates some guidelines for acne treatment based on lesion type.[39]

There are three lesion types.

- **Comedonal lesions –** prescribe one of the following:
  - Topical retinoid
  - Benzyl peroxide
  - Salicylic acid
  - Azelaic acid

  If results are unsatisfactory, increase strength or change medication
- **Mixed comedonal lesions and papulopustules –** prescribe one of the following:
  - Retinoid + topical antibiotic
  - Retinoid + benzyl peroxide
  - Retinoid + benzyl peroxide + topical antibiotic

  If results are unsatisfactory, azelaic acid + benzyl peroxide prescribe retinoid + course azelaic acid + topical antibiotic of oral antibiotics
- **Cystic lesions –**
  - Prescribe: Course of oral antibiotic + mixed comedonal-papulopustular topical therapy
  - If results are unsatisfactory, consider whether the patient is a candidate for oral isotretinoin therapy
  - If results are unsatisfactory, consider possible endocrinopathy – then either:
    - Treat endocrinopathy OR
    - If no sign of endocrinopathy is found, consider repeat course of oral isotretinoin.

Hormonal therapies for acne include systemic medications with various mechanisms: androgen receptor blockers (e.g., spironolactone, cyproterone acetate, chlormadinone, and flutamide); adrenal androgen production blockers (e.g., glucocorticoids); or ovarian androgen production blockers. (e.g., gonadotropin-releasing agonists and oral contraceptives).[40]

Androgen receptor blockers

Spironolactone

Spironolactone is the most utilised antiandrogen therapy in the United States.[41] Spironolactone blocks androgen receptors and inhibits 5-α-reductase. Spironolactone may reduce the severity of acne when dosed 50–200 mg/day over a three-month period but generally, much lower doses are required to treat acne, such as 25–100 mg/day (25 mg/day, 25 mg, twice daily, or 50 mg twice daily), in contrast to the higher doses required to treat androgenetic alopecia or hirsutism.[41] Most acne patients experience clinically significant improvement with three months of therapy.[42]

Side effects of spironolactone tend to be transient and include menstrual irregularities (in as many as half of treated patients). Usually, this is oligomenorrhoea or irregular menstrual bleeding but may, less often, manifest as hypermenorrhoea. Often, these side effects resolve within two to three months of continued therapy.[42] Oral contraceptives may help decrease the side effects such as dysmenorrhoea, irregular menses, and breast tenderness. These side effects are dose dependent and common

with spironolactone use.[43] Additional side effects include hyperkalaemia, nausea, dizziness, or polyuria (which may resolve in one to two weeks of continued therapy), and vertigo (which may necessitate discontinuation of therapy).[42] Pregnancy must be avoided as there is a risk of feminisation of the male foetus.

Cyproterone acetate

Cyproterone acetate, a progestational antiandrogen, is an androgen receptor blocker. It is available and widely used as part of a combination oral contraceptive pill (OCP).

Chlormadinone acetate

Chlormadinone acetate is a progesterone derivative, originally developed for progestin replacement therapy, but it is presently used in Europe as a component of combination OCPs, which contain ethinyloestradiol 0.03 mg and chlormadinone acetate 2 mg. Like cyproterone acetate, it blocks the androgen receptor of the pilosebaceous unit via competitive inhibition[44] as well as inhibits the endogenous secretion of gonadotropin.[45] Most common side effects are similar to other combined OCPs and include headache in 24% of patients, breast tension in 19%, dysmenorrhoea in 10%, and nausea in 10%, although these are most often in the first three to four cycles of starting the medication.[44]

Flutamide

Flutamide is an androgen receptor blocker that is approved for the treatment of prostate cancer. Side effects include dry skin in as many as 70% of treated patients; hot flushes and increased appetite in about a quarter of patients; headaches, fatigue, and nausea in > 10%; and, less often, dizziness, decreased libido, and breast discomfort.[45] Monthly liver function tests for the first four months of therapy are recommended and periodically thereafter.

Adrenal androgen production blockers

In low doses, glucocorticoids suppress adrenal production of androgens and are prescribed in individuals with elevated serum DHEAS levels, which may be associated with 11- or 21-hydroxylase deficiency. Prednisone 2.5 mg or 5 mg or dexamethasone 0.25–0.75 mg may be administered every day or every other day at bedtime.[5] Adrenal suppression is possible, especially if dexamethasone is used, and can be screened with ACTH stimulation test, two to three months after starting therapy.[7,46] Duration of therapy is limited by the long-term side effect of osteoporosis and should therefore be limited to six months.[46]

Ovarian androgen production blockers

Gonadotropin-releasing hormone agonists block androgen production by the ovary *via* inhibition of the feedback loop that controls the pituitary's release of FSH and LH. Gonadotropin-releasing hormone agonists include buserelin, nafarelin, and leuprolide and may be used to treat acne in the presence or absence of endocrine abnormalities.[40] Side effects may limit therapy and mimic menopause, with low oestrogen, headaches, and bone loss.[46] OCPs, with a combination of oestrogen and progestin, are commonly used worldwide in the treatment of acne. The most commonly used oestrogen is ethinyloestradiol (EE).[45] Each generation of progestins has varying degrees of androgen cross-reactivity, with the potential to aggravate acne or worsen androgen-related conditions; however, the levels required to do so tend to be higher than those found in modern OCPs.[46] Second-generation progestins with low androgenic activity include ethynodiol diacetate, norethindrone, and levonorgestrel, while third-generation progestins have the lowest of all androgenic activity, and include borgestimate, desogestrel, and gestodene. Drospirenone is derived from spironolactone, so its antiandrogenic and antimineralocorticoid properties can be used to improve acne and hirsutism, as well as mitigate the fluid retention associated with some OCPs due to oestrogen.[46]

Side effects of OCPs include mood changes, decreased libido, headache, breast tenderness, and irregular menstrual bleeding (typically spotting between cycles).[47] Weight gain is often indicated as a side effect of oral contraception and may deter women from starting the medication. Hormonal therapies (e.g., ethinyloestradiol or the antiandrogen cyproterone acetate) is useful in women who suffer from moderate to severe acne. They are prescribed in combination with a non-androgenic progestogen (e.g., norgestimate or desogestrel) as a combined oral contraceptive. Serum flow is decreased by 40%, but improvement can take as long as three to six months. Progestogen-only contraceptives can exacerbate acne.

Isotretinoin

Isotretinoin is indicated for severe acne and gives an almost 100% probability of complete remission. High doses can produce prolonged remission. Side effects include dry lips, nose and eyes, increased plasma triglycerides, photosensitivity, headaches, and myalgia. It has also been reported and well publicised that cases of mood disorders are associated with isotretinoin. Teratogenesis is a problem, and although the half-life of the metabolites is less than two days, conception should be totally avoided during treatment and for one month after stopping treatment.[10] Treatment is usually deemed complete when a cumulative dose of 120–150 mg/kg has been reached. Isotretinoin therapy must be monitored carefully because adverse effects include potent teratogenicity, hypertriglyceridaemia and pancreatitis, hepatoxicity, blood dyscrasias, hyperostosis, premature epiphyseal closure, and night blindness.[38] Patients should also be warned about suicidal tendencies and psychosis.[48]

Treatment of children and pregnant women

The treatment of acne in children is similar to that in adults. Topical therapies may be more irritating in children, so initiation with low concentrations is recommended. Systemic treatments should be reserved for more extensive cases. Erythromycin is preferred over tetracyclines for children under nine years of age, because tetracyclines can affect growing cartilage and teeth. Although treatment with isotretinoin has numerous potential minor side

effects in patients of all ages, an uncommon complication in young patients is premature epiphyseal closure. This generally occurs when isotretinoin is administered in high doses, thus limiting long-term therapy. Selecting appropriate treatment in pregnant women can be challenging because many acne therapies are teratogenic; all topical and especially oral retinoids should be avoided. Oral medicines such as tetracyclines and antiandrogens are also contraindicated in pregnancy. Topical and oral treatment with erythromycin may be considered.

Topical antibiotic medications remain first-line agents for the treatment of patients with mild-to-moderate acne. For more severe cases, penicillin or cephalosporins are the most reasonable next step, with macrolides as a second-line oral treatment option. Severe cases of nodulocystic acne or acne conglobata with severe psychosocial impact may require controlled courses of corticosteroid medications to ameliorate symptoms. Oral metronidazole represents a potential alternative, third-line oral therapy that may be used, in combination with topical treatments and low doses of prednisone.[49]

The choice of treatment for acne is dependent on the severity of the presenting acne. Initially, management of non-inflammatory comedones should be with topical treatment. Topical retinoids are increasingly used for all types of acne, except severe acne, or as maintenance treatment, with azelaic acid as an alternative option. For early inflammatory lesions, a topical antibacterial or benzoyl peroxide is recommended, as either single or combination agents. Oral antibiotics are helpful for moderately severe acne, with oestrogen or antiandrogen therapy (as a combined oral contraceptive) as alternatives for women. Systemic treatment with isotretinoin is used in severe unresponsive acne but is also an option for moderately severe acne. The most common reason for treatment failure is a lack of adherence to the recommended treatment regimen.

Counselling

- Counsel the patients on the correct use of isotretinoin; inform female patients that they should sign the form, of which a copy is placed in their patient file, stating that they will not become pregnant during the course of the treatment, and for one month thereafter. Inform them of the serious teratogenic effect of isotretinoin's use.
- Encourage sales of a sunblock (SPF 50) and lip balm when isotretinoin is prescribed. This will aid in protecting the skin against the sun and provide moisture to dry lips.
- Encourage patients not to pick on their acne scars as this will lead to spreading of the acne. Also, encourage patients to wash their hands when they touch the areas affected with acne.
- Advise patients to use topical antibacterials together with either benzoyl peroxide or topical isotretinoin as the antibacterial penetration thereof is increased.
- Enquire if the patient is taking any medications to eliminate medicine causing acne-like skin eruptions. Medications implicated include the following: lithium, oral contraceptives (e.g. those that have high progestogen levels), phenytoin, azathioprine, and rifampicin. If the patient is using these treatments, additional counselling should be provided for management.
- Inform the patient that they should see a general improvement after eight to 12 weeks of treatment with simple anti-acne treatment and that should this fail, it is best for them to seek the assistance of a general practitioner or dermatologist.
- Educate the patient using benzyl peroxide about its side effects of drying, burning, and peeling of the skin and that they can stop the treatment for a day or two before starting it again. Patients should start treatment at the lowest concentration available, especially if they suffer from sensitive or fair skin.
- Explain and educate the patient about the condition and state that the aim of the treatment is to be cosmetically advantageous as well as to prevent permanent scarring. Should diet be implicated, the necessary dietary changes need to be made, and psychological factors need to be eliminated as far as possible.
- Explain to all women of childbearing age using acne treatments that:
  - All topical acne therapy should be stopped if pregnancy occurs.
  - Topical retinoids should not be prescribed for pregnant women, women wishing to become pregnant, or nursing women.
  - Oral tetracycline should not be taken by pregnant or nursing women. The only FDA-approved medication to treat acne during pregnancy is azelaic acid (category B) and should be used with caution in nursing women.
  - It is imperative for women who are starting oral isotretinoin (category X) to practice two forms of birth control, participate monthly in pregnancy tests, and not become pregnant for at least one month after cessation of therapy due to oral isotretinoin's known teratogenic effects.
- Explain to patients that they should apply basic skincare to manage their acne. The skin should be gently cleaned twice daily, and comedogenic creams and cosmetics should be avoided.
- Instruct patients to apply exceedingly small amounts of retinoids initially and explain that optimal response should occur after 12 weeks.
- Mention to the patient that when they are using benzoyl peroxide that they should take note that this medication has bleaching properties.
- Emphasise to the patient that when applying a combination topical therapy, such as benzoyl peroxide and retinoids, that the combination of these medications is more effective than either therapy applied alone. However, these medications should be applied at separate times, as benzoyl peroxide may oxidise a retinoid, such as tretinoin if applied simultaneously.[50]
- Educate and remind patients to avoid harsh washing of their skin (avoid scrubs or exfoliating devices) as this may damage the

natural skin barrier function. Cleansers with a pH of 5.5 should be favoured over traditional detergents (e.g., soaps), allowing for a gentle cleansing of the skin and for a reduction of the particle load on the skin in the evening. The optimal frequency of cleansing should be twice a day.

- Pharmacists can play an important role in the education of a patient suffering from acne as well as being a pillar of support for them. They can also refer patients to the relevant people/instances that can aid in the alleviation of depression, suicide idealisation and low self-esteem.

Conclusion

Acne vulgaris is quite a common skin condition that can occur in children, adults, and pregnant women. This condition is caused by an excess secretion of sebum that triggers acne. This promotes the growth of *C. acnes*. Treatment depends on the severity of the acne and can be done topically with retinoids, azelaic acid, benzoyl peroxide or topical antibacterials, or systemically with oral antibacterials, hormonal therapies or isotretinoin. The pharmacist plays an important role not only in the dispensing of acne medications but also in the education of patients about correct skin care products and medications used, especially in women of childbearing age.

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All the right friends in all the right places

Kaajal Chetty

President, SAAHIP

When we paint the ideal picture of patient care, it should be detailed with the brushstrokes of a multidisciplinary team. This is a team comprising of healthcare workers from different disciplines who each provide specific services to the patient. Easy to define, difficult to enforce!

Kaajal Chetty

With the disproportion of services in the private and public sectors, only a handful of patients benefit from such comprehensive care.

Undoubtedly, efforts are being made at various institutions to create and maintain 'best practices', including the promotion of a multidisciplinary approach to patient care. Small, steady steps are better than large, unstable leaps, so every initiative is appreciated.

For such an effort to be successful, one of the key elements that the team needs to master is clear and effective communication. Communication between the professionals themselves and with the patient. A well-designed treatment plan on paper is worthless if a patient goes home not understanding what needs to be done.

The time we spend per patient is hardly enough to convey every detail we would like to include, but it is imperative that when a patient leaves the pharmacy, they understand their condition and corresponding treatment. Remember to minimise the heavy, scientific lingo for simpler, easy-to-understand explanations. Always encourage the asking of questions. Forgive the patient who argues with you for wasting their time.

There may be many opportunities, scattered in the day, to interact with other healthcare professionals aside from formal multidisciplinary ward rounds. Not all facilities are able to undertake such ward rounds due to the shortage of staff and scheduling conflicts. Whenever the interactions do take place, we need to remember to treat each other with respect, bearing in mind each other's roles and responsibilities. Never fear offering suggestions or comments on a patient's treatment protocol. Healthy discussions between healthcare professionals are always welcomed.

We must not forget our 'friends' in higher places – the Heads of Departments, Heads of Pharmaceutical Services, provincial Members of the Executive Committee, Minister of Health and various stakeholders. Communication through the right channels can be beneficial. When this 'friend' requests your comment on policies and protocols, please use the opportunity to mould the face of healthcare for the better. What you say matters!

Pharmacists are special. You are capable of building relationships and making 'friends'. You possess the radiance to encourage teamwork and forge relationships with fellow healthcare professionals and with patients. So go for it … Shine on, my friends!

Warfarin toxicity caused by drug-drug interactions

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Introduction


Monet van Antwerpen

Drug-drug interactions (DDIs) can cause a variety of drug therapy problems resulting in reduced effectiveness of a medication, increased toxicity of a medication, as well as causing adverse drug reactions.[1] DDIs are considered preventable drug therapy problems, but can still lead to increased risk of hospitalisation, prolonged hospital stays, increased health care costs and increased risk of morbidity and mortality. Factors associated with an increased risk of a patient experiencing DDIs include the patient's age, gender, education, comorbidities, and multiple prescribed medicines. While prescriptions of more than one drug for a patient are common, the incidence of potential drug interactions occurring is approximately 40% in patients taking at least five drugs and increases to 80% for patients taking seven drugs.[2,3]

Warfarin is considered to be one of the drug products that most frequently causes DDIs where some level of intervention is required to change the patient's drug regimen. Warfarin is highly susceptible to drug interactions both due to its high affinity for protein binding and its metabolism through cytochrome P450 enzymes, including CYP2C9 and CYP3A4. The variability of its metabolism increases the risk of subtherapeutic or supratherapeutic levels which can lead to adverse events such as bleeding. A study conducted in a district hospital in Cape Town, South Africa found that only 48.5% of patients on warfarin therapy achieved target therapeutic range, with the prevalence of haemorrhagic events being 14%.[4-6]

The commonly known drug-drug interactions that potentiate the effect of warfarin are summarised in Table I.

Case presentation

This case was encountered at New Somerset Hospital, a public sector district hospital in the Western Cape, South Africa. It emphasises the role of a pharmacist in identifying drug-drug interactions and managing the resulting adverse effects as part of the multidisciplinary team.

Patient presentation

Ms SP is a 31-year-old female with a body mass index (BMI) of 17.7 kg/m^2. Her medical history included an HIV-positive status with

Table I: Drug interactions that alter warfarin concentrations[7-10]

Mechanism		Drugs	
CYP 2C9 inhibitor	The primary enzyme responsible for warfarin metabolism is inhibited, slowing down the metabolism of warfarin. Interactions involving CYP 2C9 are clinically more important, as it is responsible for metabolism of the S-enantiomer of warfarin which is five times more potent than the R-enantiomer.	Amiodarone Cimetidine Clopidogrel Cotrimoxazole Efavirenz	Fluconazole Fluoxetine Isoniazid Omeprazole
CYP 2C9 inducer	The primary enzyme responsible for warfarin metabolism is induced, increasing the metabolism of warfarin.	Ritonavir Rifampicin	St John's Wort
CYP 3A4 inhibitor	The enzyme partially responsible for warfarin metabolism is inhibited, slowing down the metabolism of the R-enantiomer of warfarin and increasing drug concentration.	Cotrimoxazole Fluoroquinolones Metronidazole	Macrolides Ritonavir Fluconazole
CYP 3A4 inducer	The enzyme partially responsible for warfarin metabolism is induced, increasing the metabolism of the R-enantiomer of warfarin, and reducing drug concentration.	Carbamazepine Ethanol Barbiturates Nevirapine	Griseofulvin Rifampicin St John's Wort
Protein displacement	Highly protein bound warfarin is displaced causing increased serum concentrations.	Phenytoin Sodium valproate Ibuprofen	Amlodipine Losartan Quinidine

a CD4 count of 33 cells/cm^3 and unknown viral load, as well as recent diagnoses of *Pneumocystis jirovecii* pneumonia (PJP) and cryptococcal antigenemia, for which she was still undergoing treatment.

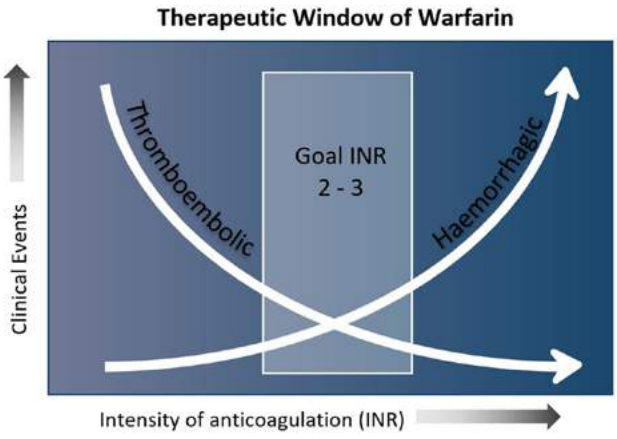
Ms SP presented to the emergency department of the hospital with a generalised tonic-clonic seizure and was subsequently diagnosed with superior sagittal sinus thrombosis confirmed on a computed tomography scan of the brain. A treatment regimen of sodium valproate and warfarin was initiated while continuing with her treatment for PJP and cryptococcal antigenemia, including cotrimoxazole, prednisone and fluconazole.

The current complaint occurred on day 4 of her warfarin therapy, where the patient developed nose bleeds and an international normalised ratio (INR) reading of 13.39 was recorded. A diagnosis of warfarin toxicity was made with the likely cause identified as drug-drug interactions.

Warfarin toxicity

Warfarin is an anticoagulant with a narrow therapeutic index. It competitively inhibits enzymes responsible for the cyclic vitamin K interconversion in the liver resulting in a vitamin K deficiency, leading to reduced levels of coagulation proteins, and clotting factors and resulting in an increased risk of bleeding. Patients at higher risk of bleeding while on warfarin therapy include the elderly (≥ 65 years), those with acute illness, comorbid conditions, variable vitamin K intake through diet, those with a medical history of gastrointestinal bleeding or peptic ulcer disease and elevated INR levels of > 4.[4,11]

Warfarin toxicity is defined as INR >3 or > 3.5 in patients with mechanical heart valves. Some patients may present with bleeding including minor bleeding such as epistaxis, purpura, and occult bleeding from the gastrointestinal tract, or with major haemorrhage including intracranial haemorrhage, gastrointestinal bleeding, haematemesis, intraocular bleeding and haemarthrosis. However, asymptomatic presentation of warfarin toxicity is more common.[12]



Supratherapeutic INR readings during warfarin therapy can be caused by dose changes, inadequate dose titration, drug interactions, diet changes and genetic polymorphisms. Liver disease and alcohol use can also influence the half-life of warfarin and the time to steady-state concentrations. The time to peak effect of the drug is typically 36–72 hours with a duration of 2–5 days following cessation of the warfarin, and potential delays in INR have been seen for 12 hours following dosing, with coagulopathy seen for up to 9 days.[8]

According to the South African Standard Treatment Guidelines and Essential Medicines List,[13] warfarin toxicity should be treated based on severity which is classified according to INR levels and the presence of bleeding. The treatment options are described in Table II below.

Table II: Management of warfarin toxicity[13]

Symptoms	INR level	Treatment
No bleeding	5–8	Stop warfarin If high bleeding risk: Vitamin K1 po 1–2.5 mg for 1–2 days Monitor INR
	> 9	Stop warfarin Vitamin K1 po 2.5–5 mg for 1–2 days Monitor INR
Significant bleeding	> 5	Stop warfarin Lyophilised plasma IV 15 ml/kg *OR* Fresh frozen plasma 15 ml/kg Followed by: Vitamin K1 IV 10 mg diluted in 100 ml NaCl 0.9% over 20 min Monitor INR

Once the patient's INR levels have returned to within normal range (2–3), warfarin may be restarted. The initial cause of the toxicity should be addressed and resolved to prevent rebound toxicity. Reinitiating warfarin should be done cautiously with the aid of a dosing nomogram[14] to guide starting doses, dosing adjustments and omissions to ensure INR levels remain within the normal therapeutic range with continuous therapeutic monitoring.[15] A warfarin dosing nomogram can be accessed at the QR code shown below.

Non-pharmacological management includes counselling the patient on safe warfarin use upon discharge.

Counselling about adherence, adverse effects such as bleeding, and taking warfarin at the same time each day ensures that the patient has a good understanding about the benefits and risks of warfarin

therapy. Further counselling on diet, including limiting alcohol intake to a maximum of two drinks daily, avoiding grapefruit juice and ensuring a constant vitamin K intake from week to week should also be included. To avoid drug interactions from occurring, patients should also be counselled on avoiding over-the-counter nonsteroidal anti-inflammatory drug (NSAID), herbal products such as St John's Wort and traditional medicines.[9,13]

Clinical dilemma

Ms SP was receiving warfarin therapy while also receiving sodium valproate, fluconazole and cotrimoxazole therapy – all agents that potentiate the effect of warfarin through different mechanisms (Refer to Table I).

The following medication-related problems were identified on review of Ms SP's prescription chart in the medical ward:

1. Ms SP experienced nose bleeds with a supratherapeutic INR of 13.39 while receiving warfarin therapy.
2. Her fluconazole dose (1.2 g) for the treatment of cryptococcal antigenemia was too high as she had already completed 14 days of induction therapy; this was likely to be interacting with her warfarin therapy.
3. Her cotrimoxazole dose for the treatment of PJP was too high for her weight, and this would also interact with warfarin to increase its effect.
4. She also required additional drug therapy in the form of a suitable combination antiretroviral regimen, as she was treatment naïve.

Through discussion with the medical team, the following changes were recommended:

1. Discontinue warfarin and administer an immediate dose of vitamin K 5 mg orally.
2. Reduce the fluconazole dose from 1.2 g to 800 mg orally daily for 8 weeks to complete the consolidation phase of treatment of cryptococcal meningitis.
3. Reduce the cotrimoxazole dose from 320/1 600 mg to 240/1 200 mg 6 hourly for the next two days to complete 21 days of PJP treatment, and then reduce it to 160/800 mg daily for opportunistic infection prophylaxis until her CD4 count is above 200 cells/cm^3.
4. Add a fixed dose combination of dolutegravir/lamivudine/tenofovir at a dose of 50/300/300 mg orally once daily.

These recommendations were accepted, and doses were appropriately adjusted. Once Ms SP's INR levels returned to within the normal range of 2–3, the medical team reinitiated her on 2.5 mg of warfarin daily. The patient experienced rebound toxicity and her INR levels increased once more to 10.28. Her warfarin toxicity was managed by discontinuing warfarin therapy.

Patient outcome

Once INR returned to within therapeutic range (2–3), Ms SP was discharged from the hospital after receiving counselling on the use of warfarin going forward. A follow-up appointment at her local community health centre (CHC) was booked before discharge, where warfarin therapy was reinitiated at a twice-weekly dose of 2.5 mg. Her INR was monitored monthly and quickly stabilised within the therapeutic range.

Role of the pharmacist

As experts in medicine, pharmacists can provide information and resources about warfarin therapy as part of multidisciplinary teams. Providing recommendations on the use, administration and monitoring of warfarin to medical practitioners and nurses can assist in avoiding adverse events in a hospital setting. Encouraging an individualised approach to dosing with the aid of nomograms and monitoring the patient's response to therapy is another way in which a pharmacist can contribute to the team and ensure that warfarin is being prescribed safely and rationally.

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Tribute to Lee Baker

1952–2022

Lee Baker obtained her DipPharm in 1975 and registered with the Pharmacy Council as a pharmacist in January 1977. In 1987, she found her métier when she joined Geraldine Bartlett at the newly-established TPS Drug Information Centre. In 2001, when the new owners of Medikredit decided to no longer sponsor an independent medicines information centre, Lee founded her own centre – the Amayeza Info Services. She retired from Amayeza at the end of March 2022.

Not only was Lee Baker a prominent pharmacist, respected for her knowledge and professionalism, but she was recognised in the travel medicine area as a leader, nationally and internationally. She was the immediate past President of the South African Society of Travel Medicine (SASTM). At an international level, she was a member of the Leadership Council of the Pharmacist Professional Group of the International Society of Travel Medicine.

She served on national malaria advisory bodies for more than 20 years, initially as a member of the Malaria Advisory Group, and then as a member of the ministerially-appointed South African Malaria Elimination Committee (SAMEC). She was a valued member of the sub-committee for access to treatment and chemoprophylaxis (SCAT), where she spearheaded efforts to down-schedule doxycycline and atovaquone-proguanil, enabling their prophylactic initiation by pharmacists.

Lee also advocated unceasingly for access to free malaria chemoprophylaxis in the public sector, and was instrumental in the development of proposals to the National Essential Medicines List Committee in this regard. That change is in the final stages of implementation at present. Under her guidance, Gauteng first established dedicated travel clinics, and free malaria chemoprophylaxis is now being rolled out across public sector health facilities.

In 1989, Lee joined the PSSA Southern Gauteng branch, with the Academy of Pharmaceutical Sciences (APSSA) as her primary sector. She was elected to the Southern Gauteng branch committee, and was a regular presenter at continuing professional development events arranged by the branch, usually focused on the prevention and treatment of malaria. Lee was also a frequent contributor of articles for the Golden Mortar on the same subject.

From a PSSA national point of view, Lee Baker contributed regularly to continuing professional development review articles in the South African Pharmaceutical Journal (SAPJ) over an extended period. In 2011, the SAPJ published a celebration of 10 years of the Amayeza Info Services.

Lee Baker was a key component of South Africa's independent medicines information capacity for 35 years. She founded and operated Amayeza Info Services as a standalone medicines information resource for more than 20 years, until her retirement in 2022. Tragically, Lee succumbed to complications of COVID-19 just a month after retirement.

The PSSA recognised her contribution by awarding her Fellowship of the PSSA, albeit posthumously. This is a reflection of the esteem in which she was held by her colleagues, in pharmacy and in medicine.

The PSSA extends its sincere condolences to her family.

New Sanofi GM poised to transform Southern Africa medical and pharma industry

Kagan Keklik has taken the reigns as General Manager South Africa & Country Lead of multinational pharmaceutical and healthcare company, Sanofi, in South Africa, at a time when revolutionary technology and medical interventions are set to change lives across Africa.

With all the business acumen needed, a passion for science and expertise across several therapeutic areas and products, Keklik is already inspiring excellence in the 500 plus workforce that he leads in South Africa.

Keklik has over 20 years of experience in the pharmaceutical sector where the positions he has held have spanned from managing products to leading teams in the Middle East, Eurasia, and South Asia. He has been with Sanofi for nearly 13 years, making him well-poised to take the company to new heights.

"Sanofi is dedicated to finding answers for patients by developing breakthrough medicines and vaccines. Our purpose is to chase the miracles of science to improve the lives of patients, partners, communities and our own people. We provide potentially life-changing treatments and life-saving vaccines to millions of people as well as affordable access to our medicines in some of the world's poorest countries," says Keklik.

Keklik is excited about the potential of the South African market. "South Africa is considered the gateway to the African continent and is an important market for the Sanofi Group. The people are driven and dynamic and there are great opportunities for growth. We are passionate about knowledge and technology transfer to ensure the local manufacturing of medicines. We sincerely look forward to helping to make a difference and I look forward to working with my team to drive change in the region," says Keklik.

Keklik is a great proponent for forging important alliances, such as the strategic partnership with South African manufacturer, Biovac, for the local manufacture of vaccines through the transfer of manufacturing excellence, skills, and knowledge.

Kagan Keklik, General Manager South Africa & Country Lead, Sanofi South Africa

Keklik's vision takes this even further: "As a world leader in the development and delivery of vaccines, we fully support continued investment in localised manufacturing and the sustainability of local vaccine supply. Through long-term partnerships such as the one we have with Biovac, we can ensure that South Africa can be a manufacturing hub that will improve the distribution of vaccines into neighboring countries."

Supported by a strong team, Keklik is enthusiastic about unlocking not only the potential of the region but also of Sanofi itself. He sees himself as a transformative leader and believes in inspiring and empowering individuals and teams to achieve the company's goals. At the same time, he is prepared to push limits to make a difference in both the prescription and over-the-counter medication markets.

"We are focused on growth and believe this can be achieved if we lead with innovation and accelerate efficiencies. I'll be focusing on these levers over the next few years to ensure Sanofi maintains its position as a leading healthcare company, not only in South Africa, but throughout the region," says Keklik.

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