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SPECIALIST FORUM

Vol. 24 • No. 1 • January 2024

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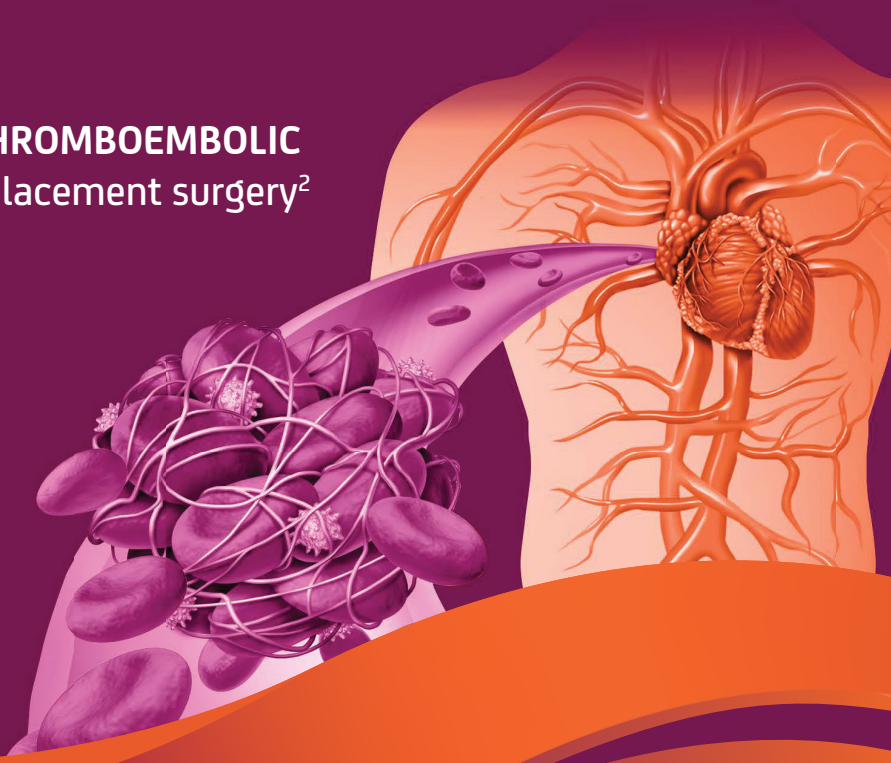

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References: 1. Data on file, IQVIA MIDAS, Patient treatment days prescribed Q2 2022
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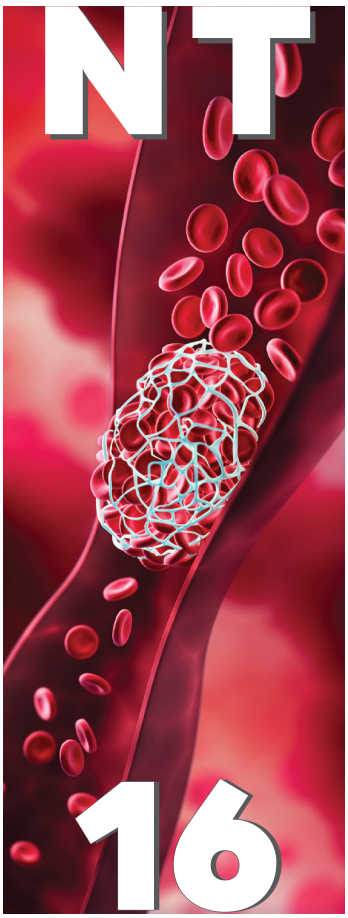

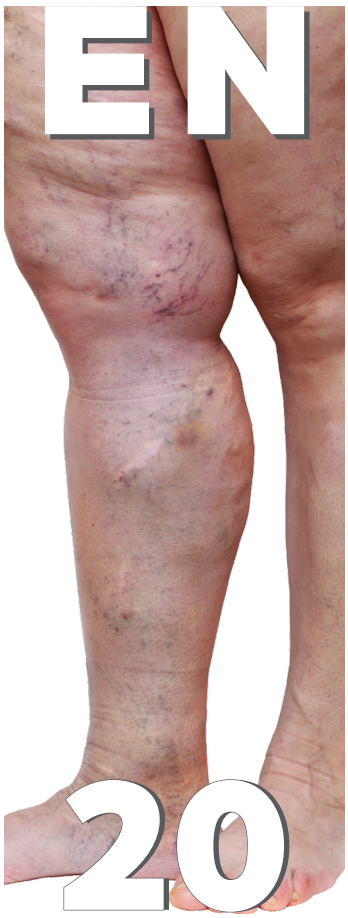

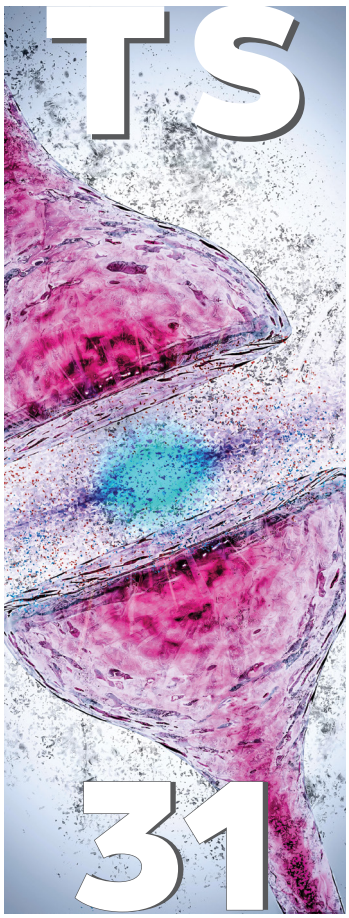

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Dive into our first issue of 2024!

Welcome to the inaugural 2024 edition! We are thrilled to embark on this new journey with you and wish you success and prosperity in abundance for the year to come. May 2024 also be filled with love, laughter and victories!

One of the highlights of our January issue is the inclusion of some of our most popular continuing professional development (CPD) articles from 2023. These articles are not just a recap, they are an opportunity for our readers to earn nine (9) valuable CPD points.

We believe in the importance of continuous learning and professional development, and what better way to start the year than by providing a platform to enhance your skills and knowledge.

On behalf of the SASREG committee, we are pleased to invite you to the SASREG Congress 2024. Our congress brings together experts and professionals with a focus on an Infertility Care: A Multidisciplinary Approach. The delegates will include reproductive medicine specialists and general gynaecologists with an interest in endoscopy or infertility, the embryologists who work in IVF laboratories, fertility nursing sisters and psychology counsellors.

With a carefully curated programme of distinguished speakers, relevant topics and interactive workshops, this congress is designed to inspire, educate, explore cutting-edge developments in the field and network opportunities.

Join us on this exhilarating journey of discovery and innovation at SASREG Congress 2024.

Don't miss our epilepsy articles. International Epilepsy Day, commemorated on 12 February this year, serves as a reminder of the global impact of epilepsy and the importance of raising awareness.

February is also recognised as Reproductive Health Month, a crucial time to focus on issues surrounding reproductive well-being. Check out our informative infographic on page 6.

Furthermore, don't forget to register for the upcoming Cardiac Arrhythmia Society of Southern Africa Symposium. The symposium is scheduled for 24–25 February in Johannesburg. Our cardiology articles take a look at atrial fibrillation and the risk of stroke, prevention of venous thromboembolism and the role of ventricular arrhythmias in sudden cardiac death.

Earlier this month we published an Oncology guide to bring you up to speed on all the latest innovations in cancer care. To access a copy online, click here.

We have developed a South African medical congress calendar for your convenience. To access your copy, click here. If you would like to see your congress featured in our calendar or if you would like to advertise, send an email to charissa.piek@newmedia.co.za

In conclusion, our January issue is not merely a collection of articles. It is a testament to our commitment to supporting and celebrating the medical community. We invite healthcare professionals to engage with the wealth of knowledge presented.

Here's to a year of learning, collaboration, and making a positive impact on healthcare.

Welcome back!

Regards

René Bosman

This article was independently sourced by Specialist Forum.

Is there still time to fix the NHI Bill?

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The adoption of the National Health Insurance (NHI) Bill by the National Assembly and National Council of Provinces has raised concerns from various stakeholders, leading to a petition by the Health Funders Association (HFA) urging President Cyril Ramaphosa to reconsider certain aspects of the proposed legislation.

Craig Comrie, chairperson of the HFA, criticized Parliament for failing to consider the implications of the Bill on citizens' constitutional rights, overall healthcare, and the South African economy. The HFA requested necessary amendments to align the Bill with the true aims of universal health coverage (UHC) and the constitution.

The South African Medical Association (SAMA) also expressed concerns about the NHI Bill, which revolve around unintended limitations to healthcare access, readiness of the healthcare system, exclusion of healthcare professionals, financial challenges, and potential impacts on medical practitioners.

What are some of the advantages and disadvantages of NHI?

According to Dr Larisse Prinsen, a senior lecturer in the Department of Public Law, University of the Free State, the implementation of NHI in South Africa has several potential advantages as well as disadvantages.

Advantages include the prospect of lowering overall healthcare costs by allowing the government to regulate prices and reducing administrative expenses. A finite determination of healthcare procedure costs without unexpected expenses or depletion of medical scheme benefits is expected.

Advantages include improved healthcare standards in hospitals and clinics, potential enhancements in services, hygiene, and safety in public hospitals, and the elimination of health-related barriers to education for children with untreated health issues are also anticipated benefits.

The NHI is also seen as a stimulus to the economy, fostering a healthier workforce through preventive care, and potentially leading to better salaries for medical practitioners in the public sector.

The promotion of equality by removing barriers to healthcare based on the ability to pay is another expected advantage, aligning with the goal of achieving socio-economic rights and addressing healthcare resource inequities in South Africa.

However, along with these advantages, concerns and potential disadvantages are also recognised. Compulsory enrollment in the NHI system may compromise individual autonomy, and the financial burden on taxpayers, especially the healthy paying for the sick, raises concerns.

Other drawbacks include uncertainty and vagueness surrounding the NHI's financial aspects, decreased financial incentives for maintaining health, potential unemployment in the medical sector, and long waiting times for elective procedures.

Additionally, concerns about a decrease in the quality of care, uncertainty regarding coverage, the potential for political motives behind the NHI, and the risk of corruption and misappropriation of funds have been raised.

The implications for South Africans vary depending on their current healthcare status. For those without medical scheme membership or in lower income groups, the NHI is seen as beneficial, providing more equitable access to healthcare services.

However, for those who belong to a medical scheme, adjustments may be required, potentially settling for lower standards while still bearing a similar or higher financial burden.

The NHI's implementation also raises questions about the future role of medical schemes, which may be limited to providing complementary or top-up cover, and the potential negation of their role in the universal healthcare landscape are still hotly debates.

NHI funding model

In response to some of the concerns about the fairness of funding everyone's healthcare needs through a few taxpayers, Dr Nicholas Crisp, deputy director General of NHI explained NHI is a health financing system designed to realise the right to health progressively. The transition to NHI will be a gradual process implemented in two phases and is expected to be fully implemented by 2026.

He emphasised that NHI is not merely a request for more funding. It involves contributions from the entire population, including indirect taxes. With regard to concerns about ministerial overreach and corruption, Dr Crisp said governance mechanisms are in place to deal with these issues. He added that the move towards a single-payer system is expected to reduce corruption.

The NHI funding framework aims to strategically utilise capabilities to purchase healthcare services on behalf of the entire population. The exclusion of the Competition Act from the NHI Bill is intended to enable monopsony (a market situation in which there is only one buyer) purchasing without breaching competition laws.

Foreign nationals' healthcare will adhere to international agreements, caring for those legally in the country, professional autonomy will not be limited, and accreditation processes will be in place.

Implications for healthcare providers

According to the National Department of Health, private healthcare providers will continue to operate, but under a different environment created by the NHI. NHI aims to regulate fees charged by private providers to prevent 'exorbitant' charges. Practices such as 'discarding patients after exhausting funds' will also not be permitted. Furthermore, under NHI, private providers cannot charge extra cash (co-payment) after NHI payments.

Private ambulance providers will no longer be allowed to only attend to medical scheme members, which adheres to constitutional provisions for emergency medical treatment.

Sources available on request. SF

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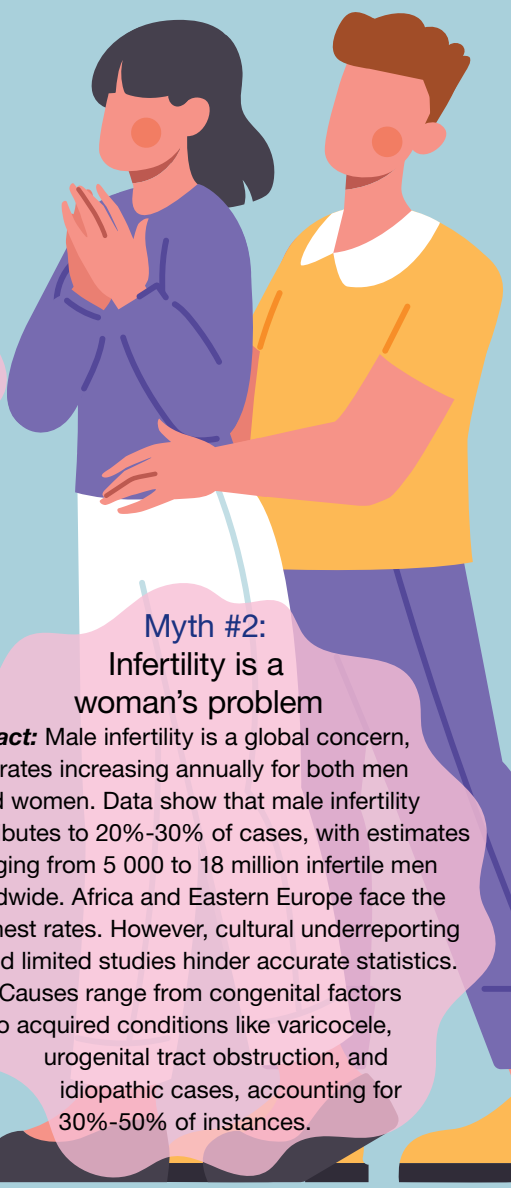
Unravelling 10 myths about infertility

Infertility rates are increasing globally, and unfortunately so has the number of unfounded myths surrounding this issue, which affects millions of couples around the world. What are the most common myths surrounding infertility?

Myth #1:
Infertility is rare

Fact: Infertility is a widespread global issue affecting >15% of reproductive-aged couples. Infertility is characterised by the inability to conceive after 12 months of regular unprotected intercourse. It impacts millions of individuals and communities worldwide, with ~48 million couples and 186 million individuals facing fertility challenges. Recent United Nations reports indicate a decline in fertility rates globally.[1]



Myth #2:
Infertility is a woman's problem

Fact: Male infertility is a global concern, with rates increasing annually for both men and women. Data show that male infertility contributes to 20%-30% of cases, with estimates ranging from 5 000 to 18 million infertile men worldwide. Africa and Eastern Europe face the highest rates. However, cultural underreporting and limited studies hinder accurate statistics. Causes range from congenital factors to acquired conditions like varicocele, urogenital tract obstruction, and idiopathic cases, accounting for 30%-50% of instances.

Myth #3:
You can't be infertile if you already have one biological child

Fact: Despite conceiving or giving birth, couples may face secondary infertility, defined as the inability to have a live birth for at least five years since the last birth without contraceptive use. Secondary infertility surpass primary cases. Factors like sexually transmitted diseases, post-abortion complications, and infections from unhygienic practices during menstruation, delivery, and postpartum periods contribute to secondary infertility. Caesarean section deliveries and other shared risk factors affect both primary and secondary infertility.

Myth #4:
Infertility is a psychological or stress-induced issue

Fact: While stress is associated with infertility, it is not solely a psychological problem, and addressing stress through psychological support may help but is not a guaranteed solution for infertility.

Myth #5:
Health and lifestyle habits do not affect infertility

Fact: Reproductive performance is influenced by diverse dietary habits and body weights. In females, inadequate nutrition, whether from underweight or overweight conditions, affects ovarian function and reduces fertility. Both male and female fertility are influenced by diet, with nutrient-rich foods positively impacting semen quality. Smoking, whether active or passive, adversely affects fertility in both genders, decreasing semen quality, increasing the risk of infertility, and impacting various stages of the reproductive process, including ovarian function and reserve. Adopting a healthy lifestyle and maintaining normal body weight improves reproductive performance.

Myth #6:
Couples who can't conceive are not having enough intercourse

Fact: The fertile window, about six days before and on the day of ovulation, enhances conception odds. While regular intercourse during this period is beneficial, very frequent ejaculations may reduce sperm potency. Abstinence plays a role in sperm quality maintenance, but the recommended duration is controversial, with potential negative effects on semen parameters beyond 10 days.

Myth #7:
Elevating legs or avoiding standing after intercourse improves conception chances

Fact: This belief lacks scientific basis. Sperm reaches the cervical canal within seconds, and their movement isn't gravity-dependent. Post-coital position does not significantly affect the sperm's journey to the egg.

Myth #8:
Using oral contraceptives for an extended period cause infertility

Fact: Using oral contraceptives for an extended period does not lead to infertility. Contrary to common fears, studies suggest that fertility declines only temporarily after stopping oral contraceptive use, possibly due to the body taking time to return to normal ovulation. In fact, research indicates that women who use oral contraceptives may experience less infertility than those who never use them. The protective effect on the endometrium and improved iron stores contribute to the positive impact of long-term use on fertility.

Myth #9:
Infertility is a message from God

Fact: Views on infertility vary across religions, with some attributing it to karma or divine trials. Religious coping, such as prayer, can have positive effects, but negative strategies like expressing dAissatisfaction with God may worsen emotional stress. However, relying solely on prayer without action may not guarantee success. Misconceptions and false beliefs about infertility's religious implications contribute to mental turmoil and stigmatisation.

Myth #10:
Adoption and treatment can cure infertility

Fact: The belief that adopting increases chances of natural conception, has been proven false by studies, which show no significant link. Another myth suggests self-medication is harmless, but many drugs can impact fertility. However, expert advice is crucial before taking medications. Contrary to the notion that infertility can always be cured, treatments vary, from medications to surgical interventions or assisted reproductive technology, with empirical treatments improving parameters but not always ensuring clinical fertility. The emotional and financial toll on individuals and couples undergoing infertility treatment can be challenging.

References available in the online issue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Moving towards personalised medicine in psychiatry

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Although the concept of 'individualised' medicine – also referred to as 'personalised' or patient-centred care – dates back to the 1960s, the term was only coined in 1999. Psychiatry 'increasingly aspires' towards personalised medicine, writes Prof Dan Stein, Chair of the Department of Psychiatry and Mental Health at the University of Cape Town, and Director of the South African Medical Research Council's Unit on Risk and Resilience in Mental Disorders, in a recent article.[1,2]

Prof Stein explains that the idea of personalised medicine is to 'tailor treatment to the individual based on their genes, environment, and sociocultural context'.[2]

What does personalised treatment mean in psychiatry?

In clinical practice, personalised care is based on shared decision-making and encourages clinicians to take time to ask patients for their own explanation of why they are experiencing symptoms, and what they consider the best way forward, notes Prof Stein.[2]

The latest American Psychological Association (APA) guideline for the treatment of depression across three age cohorts (children, adolescents and adults) states that personalised care should be based on a comprehensive assessment to identify factors that impact treatment decisions.[3]

Prof Stein agrees, stating that physicians need to take a rigorous and systematic approach to the assessment of a range of domains to effectively tailor treatment for depression.[2]

The assessment should include symptom profiles, clinical subtypes, severity, neurocognition, functioning and quality of life, clinical staging, personality traits, antecedent and psychiatric and physical comorbidities, family history, early and recent environmental exposures, protective factors and resilience, and dysfunctional cognitive schemas.[2]

According to the APA guideline clinician's accessibility, duration of treatment, location, hours of operation, available appointments, and proximity to public transportation, should also be taken into consideration.[3]

Prevalence of depressive disorders

According to the Global Burden of Disease Study 2019, published last year, psychiatric disorders are among the top 10 diseases globally. The two most common disorders are depressive and anxiety disorders. Globally, around 279.6 million people were living with depressive disorders in 2019. In sub-Saharan Africa, the prevalence of depressive disorders was 4540.4 cases per 100 000 population, compared to the global average of 3440.1 per 100 000 population.[4]

Depressive disorders: Symptoms, subtypes, severity and comorbidities

Prof Stein states the following are the most relevant in determining treatment choices:[2]

- Symptoms
- Clinical subtypes
- Severity
- Comorbidities.

Symptoms

The two most widely used classification systems for psychiatric disorders are the Statistical Manual of Mental Disorders fifth edition (DSM-5) and the International Classification of Diseases (ICD).[5]

According to the DSM-5, symptoms of depressive disorders include feelings of sadness, emptiness, or irritable mood, accompanied by somatic and cognitive changes that significantly affect the individual's capacity to function. What differs among them are duration, timing, or presumed aetiology.[6]

Symptoms must be present for at least two weeks (although most episodes last considerably longer) involving clear-cut changes in affect, cognition, and neurovegetative functions, and inter-episode remissions.[6]

Clinical types of depressive disorders

The DSM-5 differentiates between eight major depressive disorders.[6,7,8]

1. ***Major depressive disorder (MDD) including major depressive episode:*** MDD is the most common psychiatric disorder, with a lifetime prevalence ranging from 2% to 21% and will therefore be the focus of the article. Diagnostic features include depressed

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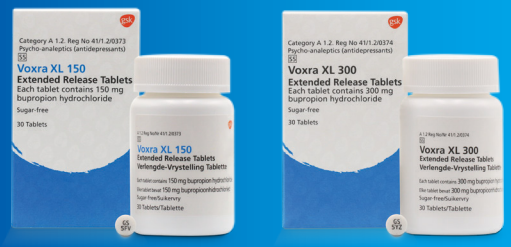

* as defined by DSM IV Criteria

"Yesterday is not ours to recover, but tomorrow is ours to win or lose" Lyndon B. Johnson

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Caution should be used in circumstances associated with an increased risk of seizures. Should be discontinued & not recommenced in patients who experience a seizure while on treatment. Observe patients closely for clinical worsening & suicidality, especially at the beginning of therapy, or at the time of dose changes, either increases or decreases. Symptoms reported in patients treated with antidepressants: anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia, hypomania & mania. Consideration should be given to changing the therapeutic regimen, including possible discontinuation, in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Neuropsychiatric symptoms, in particular, psychotic and manic symptomatology has been observed, mainly in patients with a history of psychiatric illness. Aggression, rage and violent behaviour may occur. Prior to initiating treatment, patients should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. Safety & efficacy in patients under 18 years not established. Discontinue treatment promptly if patients experience hypersensitivity reactions during treatment. Symptoms may persist after discontinuation & clinical management should be provided accordingly. Treatment in renal impairment should be initiated at reduced dosage. Should be used with caution in patients with mild hepatic impairment and reduced frequency of dosing should be considered. Closely monitor patient for possible adverse effects that could indicate elevated blood & tissue levels of drug & metabolites. A reduced frequency of dosing may be required in the elderly. Caution should be exercised in patients with cardiovascular disease. Exercise caution before driving or use of machinery until certain of effects. **INTERACTIONS:** Concomitant therapy with certain betablockers, anti-arrhythmics, SSRIs, TCAs, antipsychotics & medication metabolised by CYP2D6 should be initiated at the lower end of the dose range of the concomitant medication. Citalopram. Coadministration of drugs known to induce metabolism (e.g. carbamazepine, phenobarbitone, phenytoin) or inhibit metabolism may affect its clinical activity. Ritonavir reduces bupropion exposure. Consumption of alcohol should be minimised/avoided. Concurrent treatment with either levodopa or amantadine should be with caution. Concomitant use with Nicotine Transdermal System (NTS) may result in elevations of blood pressure. **PREGNANCY & LACTATION:** Safety not established. Epidemiological studies following maternal exposure in the first trimester have reported an association with increased risk of some congenital cardiovascular malformations, including ventricular septal defects and left ventricular outflow tract defects. Mothers should be advised not to breastfeed. **DOSAGE AND DIRECTIONS FOR USE:** The initial dose is 150 mg taken as a single daily dose in the morning. Patients not responding to this dose may be increased to 300 mg/day, given once daily. Tablets should be swallowed whole and not cut, crushed or chewed. When switching patients from SR tablets to XL tablets, give the same total daily dose when possible. A reduced frequency of dosing should be considered in patients with mild hepatic impairment. ***Children and Adolescents:*** Contraindicated in children or adolescents aged less than 18 years. ***Elderly:*** A reduced frequency and/or dose may be required. ***Renal Impairment:*** Treatment should be initiated at a reduced frequency and/or dose. ***Liver Impairment:*** Use with caution in patients with mild liver impairment - a reduced frequency of dosing should be considered. Contra-indicated in patients with moderate to severe hepatic cirrhosis. **SIDE EFFECTS:** ***Very common:*** weight loss, insomnia, headache. ***Common:*** hypersensitivity reactions such as urticaria, anorexia, agitation, anxiety, tremor, dizziness, taste disorders, visual disturbance, tinnitus, increased blood pressure (sometimes severe), flushing, dry mouth, gastrointestinal disturbance including nausea and vomiting, abdominal pain, constipation, rash, pruritus, sweating, fever, asthenia, chest pain. ***Uncommon:*** confusion, depression, concentration disturbance, tachycardia. ***Other:*** more severe hypersensitivity reactions including angioedema, dyspnoea/bronchospasm and anaphylactic shock. Arthralgia, myalgia and fever have also been reported in association with rash and other symptoms suggestive of delayed hypersensitivity; blood glucose disturbances; aggression, hostility, irritability, restlessness, hallucinations, abnormal dreams, depersonalisation, delusions, paranoid ideation; seizures, dystonia, ataxia, parkinsonism, incoordination, memory impairment, paraesthesia, syncope; palpitations; vasodilation, postural hypotension; elevated liver enzymes, jaundice, hepatitis; errythema multiforme and Stevens Johnson syndrome; twitching; urinary frequency and/or retention. **MANAGEMENT OF OVERDOSAGE:** Hospitalisation is advised. ECG and vital signs should be monitored. Ensure an adequate airway, oxygenation & ventilation. Gastric lavage may be indicated if performed soon after ingestion. The use of activated charcoal is also recommended. No specific antidote is known.

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Table 1: DSM-5 and ICD severity classifications[6,11]

Severity	DSM-5	ICD
Mild	Few, if any, symptoms in excess of those required to make the diagnosis are present, the intensity of the symptoms is distressing but manageable, and the symptoms result in minor impairment in social or occupational functioning	The presence of two or three symptoms that are distressing though the patient is likely to be able to continue with most activities
Moderate	The number of symptoms, intensity of symptoms, and/or functional impairment are between those specified for 'mild' and 'severe'	Four or more symptoms with the patient having great difficult to continue with ordinary activities
Severe	The number of symptoms is substantially in excess of that required to make the diagnosis, the intensity of the symptoms is seriously distressing and unmanageable, and the symptoms markedly interfere with social and occupational functioning	Several symptoms that are marked and distressing, typically loss of self-esteem and ideas of worthlessness or guilt. Suicidal thoughts and acts are common and a number of 'somatic' symptoms are usually present

mood, markedly diminished interest or pleasure, significant weight loss when not dieting, or weight gain, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue, feelings of worthlessness or excessive or inappropriate guilt, diminished ability to think or concentrate, or indecisiveness, recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide. Symptoms must be present nearly every day, with the exception of weight change and suicidal ideation. Other disorders with which MDD frequently co-occurs are substance-related disorders, panic disorder, obsessive-compulsive disorder, anorexia nervosa, bulimia nervosa, and borderline personality disorder.

2. Disruptive mood dysregulation disorder.
3. Persistent depressive disorder (dysthymia).
4. Premenstrual dysphoric disorder.
5. Substance/medication-induced depressive disorder.
6. Depressive disorder due to another medical condition.
7. Other specified depressive disorders include: Recurrent brief depression, short-duration depressive episodes and depressive episode with insufficient symptoms.
8. Unspecified depressive disorders category is used in situations in which the clinician chooses not to specify the reason that the criteria for a specific depressive disorder are not met and includes presentations for which there is insufficient information to make a more specific diagnosis (eg in emergency room settings).

The DSM-5 differentiations between the following specifiers or subtypes in MDD:[6]

- With anxious distress
- With mixed features
- With melancholic features
- With atypical features
- With mood-congruent psychotic features
- With catatonia
- With peripartum onset
- With seasonal pattern.

Criticism has been levelled against both the DSM and ICD classifications of psychiatric disorders. Stein *et al* point out that newer classification and assessment scales such as the Hierarchical Taxonomy of Psychopathology (HiTOP) and the Research Domain Criteria (RDoC), have emerged as alternatives to the DSM-5 and ICD classification systems, and assessments.[5,8,9]

However, according to Rugarro *et al*, the implementation of HiTOP in clinical practice is challenging and more research is needed. Hakak-Zargar *et al* state that RDoc is not intended to be a direct replacement of DSM-5 or for practical clinical use in the near future. Rather, it provides a framework for research.[9,10]

Severity

According to Zimmerman *et al*, illness severity has important clinical implications. Severity affects decisions to seek treatment, the type and intensity of treatment, and whether to continue or stop treatment. Assessment of severity is used to evaluate the outcome of treatment and may be used as meaningful endpoints in clinical practice.[11]

The severity of depression has been associated with health-related quality of life, functional impairment, suicidality, longitudinal course, and several biological variables.[11]

Three elements are used to define the severity levels of depressive disorders in DSM-5:[11]

1. Number of symptoms
2. Level of distress caused by the intensity of the symptoms
3. Degree of impairment in social and occupational functioning.

Both the DSM-5 and ICD classifications incorporate three levels of severity: mild, moderate, and severe.[6,11]

The most commonly used severity scales in clinical practice are the Hamilton Depression Rating Scale (HAM-D), the Montgomery-Åsberg Depression Rating Scale and the 9-item Patient Health Questionnaire (PHQ-9).[11]

The HAM-D score, developed more than 50 years ago, has been criticised 'for burying important features' of the DSM diagnostic criteria such as feelings of worthlessness and anhedonia, while Zimmerman *et al* state that they 'are unaware of any studies evaluating the performance of the PHQ-9 items in a sample of depressed patients presenting for treatment'.[11,12]

Comorbidities

According to Kraus *et al*, only about 65% of patients living with MDD patients have comorbidities. The most common psychiatric comorbidities associated with MDD include social phobia (31.3%), generalised anxiety disorder, (23.6%), post-traumatic stress disorder (20.6%), and obsessive-compulsive disorder (14.3%).[7]

Studies also show that patients living with chronic medical conditions have higher rates of MDD. For example, the prevalence of depression in people with chronic obstructive pulmonary disease has been estimated to be around 27%, type 2 diabetes 18% to 20%, myocardial infarction 20%, cancer 13% to 17%, and stroke 29% to 33%.[14]

Apart from these, patients who have suffered a traumatic brain injury, are living with Huntington's, Parkinson's or Cushing's disease, hypothyroidism and multiple sclerosis also have a high risk of developing MDD.[6,7]

New treatment guidelines

The APA guideline recommends psychotherapy, or pharmacotherapy with second-generation antidepressants. According to the authors of the guideline, antidepressants showed similar efficacy and therefore they abstained from recommending specific monotherapies for initial treatment.[3]

The 2022 National Institute of Health and Care Excellence (NICE) guidance

recommends some of the following treatment options for adults with less severe depression: Guided self-help, group and individual cognitive behavioural therapy (CBT), group and individual behavioural activation therapy, group exercise, group mindfulness and meditation, interpersonal psychotherapy and selective serotonin reuptake inhibitors (SSRIs) for at least six months.[15]

For patients with more severe depression, NICE recommends a combination of individual cognitive CBT and antidepressants. SSRIs, serotonin–norepinephrine reuptake inhibitor (SNRI), or other antidepressants are recommended if indicated in patients with severe depression. SSRIs are generally well tolerated, have a good safety profile, and should be considered the first choice for most patients. The guidance cautions that tricyclic antidepressants are dangerous in overdose.[15]

The guideline recommends that when depression is accompanied by symptoms of anxiety, the first priority should usually be to treat the depression. When the person has an anxiety disorder and comorbid depression or depressive symptoms, the priority should be to treat the relevant anxiety disorder.[15]

Furthermore, the guideline recommends combination treatment with antidepressants and antipsychotics (eg olanzapine or quetiapine) in adult patients living with psychotic features. If the patient does not want to use an antipsychotic, treat with an antidepressant alone.[15]

The 2023 American College of Physicians 'living' clinical guideline recommends CBT or monotherapy with a second-generation antidepressant, or combination treatment as initial treatment in patients in the acute phase of moderate to severe MDD. Monotherapy with CBT is recommended as initial treatment in patients in the acute phase of mild MDD.[16]

The following options are recommended for patients in the acute phase of moderate to MDD who did not respond to initial treatment with an adequate dose of a second-generation antidepressant:[16]

- Switching to or augmenting with CBT
- Switching to a different second-generation antidepressant or augmenting with a second pharmacologic treatment.

Treatment decisions should be personalised and based on discussions of potential treatment benefits, harms, adverse effect profiles, cost, feasibility, patients' specific symptoms (such as insomnia, hypersomnia, or fluctuation in appetite), comorbidities, concomitant medication use, and patient preferences.[16]

Improving personalised care in patients living with MDD

According to Rush *et al*, the goals of treatment are total and sustained symptom relief (or at least optimal symptom control, if sustained remission is elusive), restoration of function and quality of life (ideally to premorbid levels), and prevention or at least mitigation of the risks and impacts of relapse.[17]

Ideal outcomes should include changes in lifestyle and habits to promote medical and mental health, reduce the risk of depressive relapse, and enhance resilience to life stresses.[17]

The following are essential in personalised care:[17]

1. Share decision-making in the formulation of treatment plan.
2. Clarify and prioritise patient's goals and treatment preferences.
3. Share and align expectation as to duration of treatment, critical decision points and side effect management.
4. Provide education, information, and action plans for managing suicidal ideation, side effects, substance use, and concurrent general medical conditions.
5. Engage patient in monitoring symptoms, function side-effects and healthy activities.
6. Anticipate and plan countermoves to enhance adherence.
7. Define and counter obstacles to full recovery.
8. Develop relapse prevention/amelioration plan (eg prodrome, long-term side effects, dose management, risk reduction).

Furthermore, Stein *et al* state that a measurement-based care (MBC) approach is essential for personalised care. Aboraya *et al* define MBC as 'the use of validated clinical measurement instruments to objectify the assessment, treatment and clinical outcomes, including efficacy, safety, tolerability, functioning, and quality of life, in patients with psychiatric disorders'.[5,18]

A MBC approach is essential to any decision support system, note Trivedi and Daly, because it enables physicians to individualise and adapt decisions about patient care based on symptom progress, tolerability of medication, and dose optimisation.[19]

Research shows that compared to usual care, a MBC approach:[19]

- Improves psychotherapy outcomes
- Monitors symptom reduction in patients with psychiatric disorders, such as anxiety, depression, and bipolar
- Identifies patients who are improving and those who are deteriorating
- Improves role functioning, satisfaction with care, quality of care, and quality of life
- Enhances the therapeutic relationship and communication between providers and patients
- Improves collaborative care efforts among providers
- Improves the accuracy of clinical judgment
- Closes the gap between research and practice, and move psychiatry into the mainstream of medicine
- Enhances the clinician's decision-making process
- Enhances individualised treatment
- Is transdiagnostic and transtheoretical
- Is feasible to implement on a large scale.

According to Stein *et al,* clinical neuroscience, translational psychiatry, precision psychiatry, and personalised psychiatry have emerged, helping to articulate the conceptual foundations for a proposed psychiatric perspective aiming to replace or significantly augment current practice.[5]

Stein *et al* write: 'The proposed new paradigm views psychiatry as a clinical neuroscience, which should rest on a firm foundation of neurobiological knowledge. With advances in neurobiology, we will be better able to target relevant mechanisms and develop specific treatments for mental disorders'.

Conclusion

Personalised care improves patient outcomes. According to experts new classification systems and assessments are needed that promote personalised care, taking patients' genes, environment, sociocultural context, severity of symptoms, subtypes, and comorbidities into consideration. One approach that has been shown to improve personalised care is MBC. Guidelines recommend combination psycho- and pharmacotherapy for the treatment of depression. Novel concepts in psychiatry, which will further enhance the shift to personalised treatment, include the increasingly important role of neuroimaging and genomic research. SF

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New FDC levofloxacin-dexamethasone for post-cataract surgery: A potential turning point

Between 0.75%–0.90% of South Africans are living with visual impairments. The leading causes of visual impairments in the country are cataracts, refractive error, and glaucoma. Cataracts are the leading cause of blindness worldwide (47.8%). Sub-Saharan Africa has the highest of number people who are blind due to cataracts.[1,2]

A cataract is defined as 'the clouding of the lens of the eye, which prevents clear vision'. The risk of cataracts increases with age (from 3.9% [55- to 64- years] to 92.6% [≥80-years]). Apart from age, poor diet, exposure to sun rays, radiation, trauma, genetics, and the use of some medications have been implicated in the development of cataracts.[2,3]

Symptoms of cataracts may vary

Symptoms vary depending on the location of the opacity in the lens. If the opacity is in the core of the lens, it can cause reduced contrast vision, increased sensitivity to glare, and reduced colour perception. It can also lead to refraction changes, which can make the affected individual more myopic.[3]

If the opacity is in the cortex of the lens, it can cause similar symptoms, but they may be less severe. The opacity of the lens is slowly progressive and painless.[3]

Surgery restores vision and is cost-effective

Surgery is the most effective treatment to restore vision loss due to cataracts and is also cost-effective. During surgery, the opaque lens is removed and replaced with an artificial intraocular lens (IOL).[4]

A number of surgical techniques are available:[5]

- ***Manual extracapsular cataract extraction (ECCE):*** A traditional surgery technique in which the lens is extracted through a large incision. This technique is less expensive than other methods but has a higher risk of complications such as posterior capsule opacity (PCO), age-related macular degeneration, and corneal oedema.
- ***Manual small-incision cataract surgery (MSICS):*** A newer technique that uses a smaller incision than ECCE. This reduces the risk of complications.
- ***Phacoemulsification:*** Ultrasound-based phacoemulsification is considered the gold standard. It uses ultrasonic waves to break up the lens, which is then removed through a small incision. This technique has a lower risk of complications than ECCE and MSICS.
- ***Femtosecond laser-assisted cataract surgery:*** Another newer technique that uses a laser to create incisions and break up the lens. This technique has the potential to reduce the risk of complications even further, but it is more expensive than phacoemulsification.
- ***Refractive lens exchange (RLE):*** A procedure used to replace the lens in patients with high refractive errors or impending cataracts when laser surgery is not possible. It comes with risks like retinal detachment, which is more pronounced in patients with moderate to severe myopia. Severe hyperopia patients may experience choroidal oedema. RLE can lead to early age-related macular degeneration and open-angle glaucoma due to various factors, including changes in oxygen levels and the loss of free-radical scavenging properties.[5]

When is cataract surgery indicated?

According to the 2022 American Academy of Ophthalmology (AAO) Cataract in the Adult Eye Preferred Practice Pattern® guidance, the primary indication for cataract surgery is a significant decrease in vision that impairs an individual's ability to see, and for which surgery is likely to improve vision. Other indications for cataract removal include the following:[6]

- There is clinically significant anisometropia in the presence of a cataract
- A lens opacity interferes with optimal diagnosis or management of posterior segment pathology
- A lens causes inflammation and related secondary glaucoma (phacolytic, lens particle, phacoantigenic)
- The lens induces primary angle closure or other forms of lens-related glaucoma.

Complications associated with cataract surgery

Although cataract surgery is a common,

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A turning point in post-cataract surgical care[1]

- Potentially halves treatment duration to 7 days.* [2]
- FDC** with simple dosing post cataract surgery to support patient adherence. [1]
- Reduces exposure to antibiotic to align with antimicrobial stewardship practice. [1, 2]
- No dosage adjustment in elderly patients.

In most patients, a 7-day prophylaxis regimen of levofloxacin/dexamethasone successfully controls inflammation and prevents infection, effectively halving the amount of antibiotic used in clinical practice.* [2]

* Many ophthalmologists implement treatment for 2 or more weeks with dose tapering to prevent adverse reactions and clinical relapse. A follow-up, after 1 week, for a decision about whether to stop or continue treatment in patients still experiencing symptoms or inflammation is recommended. [1] Levofloxacin/dexamethasone for 1 week, followed by another week of dexamethasone alone was not inferior to 2 weeks of tobramycin/dexamethasone in preventing or reducing inflammation and in preventing infections. [3]

** FDC - Fixed-dose combination

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and relatively safe procedure, there are some potential complications that can occur. These complications can range from immediate to delayed.[7]

Some of the most common immediate complications include discomfort, bruising, and swelling of the eyelid, increased intraocular pressure (IOP), and allergic reactions to corticosteroid or antibiotic eye drops.[7]

A more serious complication that can occur post-cataract surgery is PCO. PCO is a clouding of the posterior capsule, which is the clear layer that surrounds the lens inside the eye.[7]

PCO can occur at any time post-surgery, but it is more likely to develop in the first few years after surgery. PCO can cause blurred vision and glare, and it can sometimes lead to the need for additional surgery to remove the cloudy capsule.[7]

Other potential complications of cataract surgery include:[7]

- ***Posterior capsule rupture/vitreous loss:*** This can occur if the posterior capsule tears during surgery. This can lead to severe vision loss and other complications such as retinal detachment.
- ***Cystoid macular oedema (CME):*** A swelling of the macula, which is the part of the retina responsible for central vision. CME can occur post- cataract surgery, and it can cause blurred or distorted vision.
- ***Endophthalmitis:*** A serious complication of cataract surgery involving microorganisms that enter the eye. Risk factors include rupture of the posterior capsule or the need for anterior vitrectomy during the procedure, >85-years, and male. Higher rates of endophthalmitis were found in patients undergoing intracapsular cataract extraction compared to extracapsular cataract extraction. Staphylococcus epidermidis is the most common infectious organism since it is native to the eyelid, skin, and conjunctiva and can seed the eye during the procedure.
- ***Vitreous/suprachoroidal haemorrhage:*** A sight-threatening complication that is often associated with incisional intraocular surgery. Risk factors determined for hemorrhage include myopia, glaucoma, diabetes, atherosclerotic vascular disease, and hypertension.
- ***Retinal tears/detachment:*** This is a tearing of the retina, which is the light-sensitive tissue at the back of the eye. Retinal tears can occur post-cataract surgery and can lead to vision loss if not treated promptly.
- ***Lens dislocation:*** Though rare, IOL dislocation is another principal complication following cataract surgery. Improvements in the foldable IOL design have decreased the incidence of postoperative dislocation. Inadequate capsular support is the main cause of lens dislocation and typically occurs early in the postoperative period. However, late, 'in-the-bag' dislocations can occur from progressive zonular dehiscence many months after uncomplicated surgery. Management involves IOL repositioning with or without scleral fixation sutures, or replacement with an anterior chamber IOL.

FDC levofloxacin–dexamethasone has the potential to revolutionise the management of post-cataract surgery patients

Controlling complications

According to the AAO guidance, most complications occur during the post-operative period. Ophthalmologists have an ethical obligation to the patient that continues until post-operative rehabilitation is complete.[6]

To control and prevent post-surgical inflammation and to prevent infection, patients are usually treated with a fixed topical corticosteroid-antibiotic combination. Topical corticosteroids are recommended to control ocular inflammation and antibiotics can be used to prevent infection. Infection can occur at any time until complete closure of the surgical incision.[8]

According to Bandello *et al* (2020), topical treatment is generally prescribed for at least two weeks. However, Rizzo *et al* (2021) argue that decisions regarding the choice of drugs, treatment duration, and drug association are often based on ophthalmologists' personal experience and not evidence- based medicine-oriented.[8,9]

According to the authors, antibiotic resistance, and the potential side effects of prolonged use of corticosteroids should be taken into consideration when deciding on the duration of treatment, as these factors impact patient adherence to post-surgical self-care.[9]

Bandello *et al* add that prolonging the use of topical antibiotics beyond wound recovery has no convincing justification, may be useless, and could, in fact, promote bacterial resistance.[8]

In their study, Bandello *et al* compared the efficacy and safety of a short pharmacological strategy (one week) using the first approved FDC of a quinolone antibiotic (levofloxacin) and corticosteroid (dexamethasone) eye drop to standard treatment (two weeks) with tobramycin-dexamethasone eye drops to prevent and treat ocular inflammation and to prevent infection.[8]

The efficacy of levofloxacin eye drops for the treatment of local infection and dexamethasone for the prevention and treatment of inflammation, and prevention of infection associated with cataract surgery in adults is considered well-established.[10]

The study by Bandello *et al* enrolled 808 patients from 53 centres in Italy, Germany, Spain, and Russia. The primary endpoint was the proportion of patients without anterior chamber inflammation on day 15, which was defined as the end of treatment. The key secondary endpoint was the incidence of endophthalmitis.[8]

Bandello *et al* reported that the proportion of patients without signs of inflammation in the anterior chamber in the levofloxacin-dexamethasone vs tobramycin-dexamethasone arms at days four, eight, and 15 were 73.1% vs 76.8%, 85.5% vs 86.7%, and 95.1% vs 94.9%, respectively.[8]

The proportion of patients without conjunctival hyperaemia in the levofloxacin-dexamethasone vs tobramycin-dexamethasone arms at days four, eight, and 15 were 85.2% vs 82.1%, 88.1% vs 91%, 93.9% vs 95.4%, respectively. Hyperaemia was mostly mild in both groups and never severe.[8]

Only marginal differences were seen in the proportions of patients complaining of ocular pain and discomfort at days four (–0.007), eight (–0.005), and 15 (0.005).[8]

Based on these results, the team concluded that the new short pharmacological strategy was non-inferior to the standard treatment in preventing and treating ocular inflammation and preventing infection after uncomplicated cataract surgery. The new strategy also has the potential to reduce antibiotic resistance.[8]

What about pharmacokinetic interference between the two active ingredients?

The Aqueous humour concentrations after topical apPlication of combinEd levofloxacin-dexamethasone eye dRops and of its single components: a randoMised, assEssor-blinded, parallel-group study in patients undergoing cataract surgery: the iPERME study (2020) evaluated the penetration of levofloxacin and dexamethasone into the aqueous humour

after administration in combination and as single molecules.[11]

This was a randomised, assessor-blinded, and parallel-group study. Patients scheduled for cataract surgery were assigned in a 1:1:1 ratio to receive FDC levofloxacin–dexamethasone, levofloxacin, or dexamethasone eye drops.

Either test or reference drugs were instilled in the conjunctival sac twice, 90 and 60 minutes before paracentesis.[11]

A total of 125 patients completed the study. The fraction of dose absorbed in the anterior chamber was 3.8–4.2 × 10–4 for levofloxacin and 0.3–0.4 x10–4 for dexamethasone, respectively. No notable differences in the concentration of levofloxacin were found between the FDC levofloxacin–dexamethasone arm (1.970nmol/ml) and the levofloxacin arm (2.151nmol/ml). The concentrations of levofloxacin were well above the minimum inhibitory concentrations for the most frequent Gram+ and Gram– eye pathogens.[11]

Dexamethasone concentrations were slightly lower in the FDC levofloxacin–dexamethasone arm (0.030nmol/ml) than in the dexamethasone arm (0.042nmol/ml), but still within the pharmacodynamically active range in the site of action. The difference was not clinically relevant. Dexamethasone was not detected in any aqueous humour sample, suggesting its full hydrolysis to free dexamethasone.[11]

In conclusion, the results of the study confirm that no interaction is evident between the corneal penetration of levofloxacin and dexamethasone. Both agents reach pharmacologically active concentrations when instilled as FDC eye drops in patients undergoing cataract surgery.[11]

TEAEs associated with FDC levofloxacin-dexamethasone

The AAO cautions that post-operative complications associated with medications include elevated IOP with corticosteroids and allergic reactions to antibiotics.[6]

In the study by Bandello *et al* the distribution of treatment-emergent adverse events (TEAE) was similar in the two groups except for a slightly higher incidence of headache in the FDC levofloxacin–dexamethasone arm.[8]

Corneal oedema was the most common TEAE and was reported in 3.29% of the FDC levofloxacin–dexamethasone arm, and in 4.83% of the tobramycin– dexamethasone arm, but was most likely due to the surgical procedure.[8]

In the FDC levofloxacin–dexamethasone arm, 0.76% of patients reported at least one severe AE. Four patients (1.01%) in the FDC levofloxacin–dexamethasone arm and two patients (0.51%) in the tobramycin–dexamethasone arm reported serious TEAEs (fracture after a fall, a myocardial infarction, and a retinal detachment), but none of these events were treatment-related. Other observations related to safety (IOP, visual acuity, and local tolerability) were very similar in the two treatment arms. Figus *et al* reported only one TEAE in their study (mild mydriasis in the dexamethasone arm).[8,9]

In terms of safety, a 28-day animal repeated-dose toxicity study showed that the FDC levofloxacin–dexamethasone was well tolerated, with no ocular intolerabilities, changes in IOP, or histopathological alterations. FDC levofloxacin–dexamethasone also did not impact corneal opacity or permeability.[10]

Furthermore, FDC levofloxacin–dexamethasone did not cause irritation, oedema, erythema/eschar formation, acute dermal irritation, or sensitisation potential in two animal studies.[10]

Conclusion

According to Rizzo *et al*, FDC levofloxacin–dexamethasone was developed to address some of the unmet needs of patients undergoing cataract surgery.[9]

The team describes FDC levofloxacin–dexamethasone as an 'interesting' new addition to the FDC eye drop armamentarium, which currently includes two older products: Chloramphenicol–betamethasone, launched in 1964, and tobramycin–dexamethasone, launched in 1993.[9]

Dexamethasone is considered the gold standard in the management of post-operative ocular inflammation and levofloxacin has broad-spectrum activity against both Gram+ and Gram– bacteria that are most frequently responsible for ocular bacterial infections.[11]

The results of the study by Bandello *et al* suggest that FDC levofloxacin–dexamethasone may become the reference treatment and the first-line choice compared to all other therapeutic approaches adopted in the management of post-cataract patients. The recommended dose is one drop instilled into the conjunctival sac after surgery every six hours. The duration of treatment is seven days.[8,9]

According to Rizzo *et al*, the new FDC levofloxacin–dexamethasone could represent a turning point in managing patients after cataract surgery, while mostly avoiding antibiotic resistance and improving treatment adherence.[9]

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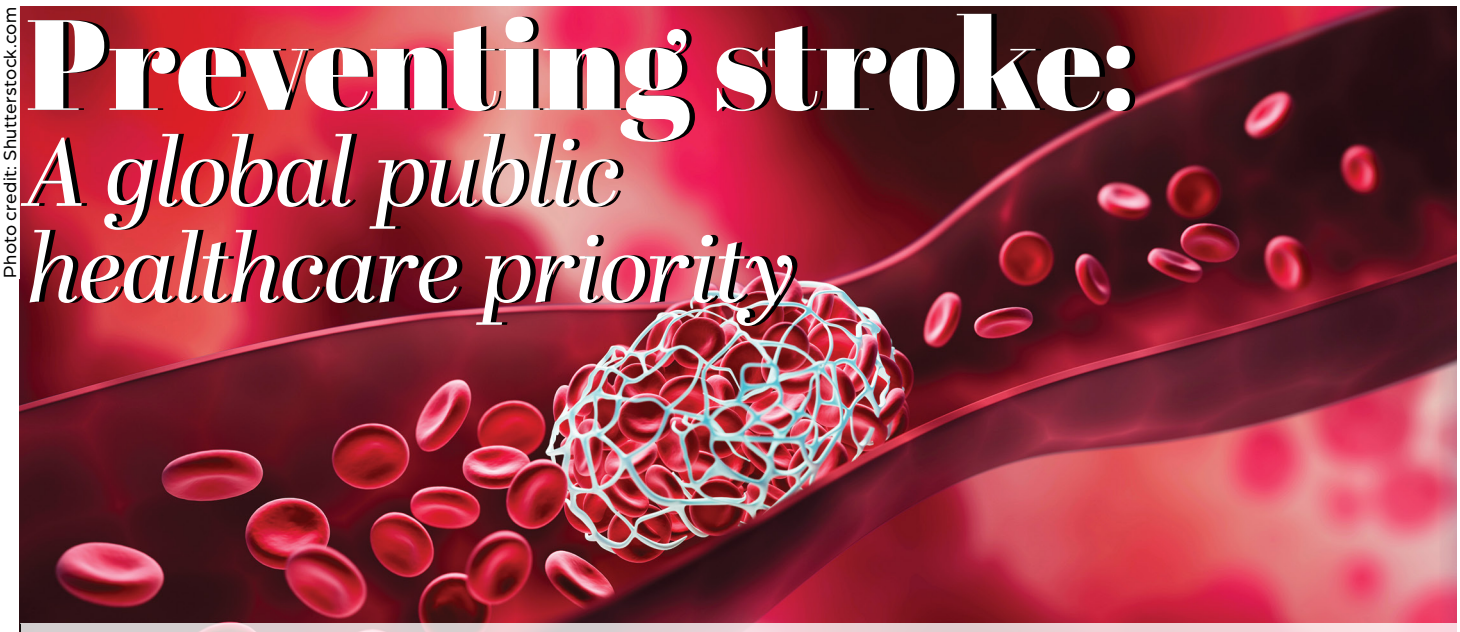
Scan for the quiz

Preventing stroke: A global public healthcare priority



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Atrial fibrillation (AFib) is the most common sustained cardiac arrhythmia in clinical practice, affecting between 1%–2% of the population. Projections show that AFib prevalence will double in the next 50 years as the ageing population increases. AFib is associated with a five-fold increased risk of stroke.[1,2,3]

Age and genetics are important risk factors for AFib. Modifiable risk factors include hypertension, diabetes, heart failure, coronary artery disease, chronic kidney disease, obesity, and obstructive sleep apnoea.[4]

Definition of AFib

The 2020 European Society of Cardiology's (ESC) guidelines define AFib as a 'supraventricular tachyarrhythmia with uncoordinated atrial electrical activation and consequently ineffective atrial contraction'. Electrocardiographic (ECG) characteristics of AFib include: [4]

- An irregular heartbeat lasting ≥30 seconds
- No discernible repeating P-waves
- No irregular R-peak-to-R-peak time intervals (when atrioventricular conduction is not impaired).

Classification: Valvular vs non-valvular AFib?

Over the past few decades, researchers have debated whether or not differentiation between valvular and non-valvular AFib should guide treatment decisions. While some guidelines still refer to valvular AFib (caused by for example a rheumatic valvular disease), and non-valvular AFib (patients in which the rhythm disturbance occurs in the absence of for example rheumatic mitral valve disease), the ESC states that differentiating between patients is confusing and these distinctions should not be used.[4,5]

Classification of AFib

AFib has the following patterns:[6]

1. ***Paroxysmal:*** If recurrent AFib reverts spontaneously. The episodes terminate spontaneously within seven days.
2. ***Persistent:*** If recurrent AFib persists, needing either pharmacological or electrical cardioversion, it is called persistent AFib. In this case, the episodes last more than seven days, and if it is associated with a rapid and uncontrolled ventricular rate, it may lead to electrical remodelling in the cardiac myocytes causing dilated cardiomyopathy. This type of AFib may present as the first episode or as a result of recurrent episodes of paroxysmal AFib.
3. ***Long-standing persistent***: AFib that has been present for more than 12 months, either due to the failure of initiation of pharmacological intervention or failure of cardioversion.
4. ***Permanent AFib:*** It is the type where a decision has been made to abort all therapies because the rhythm is unresponsive.

AFib is referred to as recurrent when a patient has two or more episodes.[6]

The complexity of AFib requires a multifaceted, holistic, and multidisciplinary approach

The ESC cautions that the severity of AFib symptoms such as shortness of breath, fatigue, and chest discomfort, can range from none to disabling. According to the society, the complexity of AFib requires a multifaceted, holistic, and multidisciplinary management approach. Patients should be actively involved in their treatment.[4]

The ESC recommends the AFib Better Care (ABC) holistic pathway (**A**nticoagulation/**A**void stroke, **B**etter symptom management, **C**ardiovascular [CV], and **C**omorbidity optimisation), which it states streamlines the integrated care of patients living with AFib across all healthcare levels and among different specialties.[4]

Compared to usual care, the ABC pathway has been significantly associated with a lower risk of all-cause death, composite outcome of stroke, major bleeding (MB), CV death, first hospitalisation, lower rates of CV events, and lower healthcare-related costs.[4]

Importance of preventing stroke

As mentioned above, patients living with AFib are at high risk of stroke. Studies show that between 15%–20% of strokes are caused by AFib. Strokes can be classified into two major categories:[7,8]

1. Ischaemic stroke occurs due to a blockage in the brain's blood supply, leading to a sudden loss of function. Ischaemic stroke can be grouped into five main pathological or etiological types, which include large artery thrombotic (20%), small penetrating artery thrombotic (25%), cardiogenic embolic (15%), and cryptogenic strokes (5%–10%), as well as strokes from other causes such as illicit drug use (20%–25%).[8p3] AFib is the leading cause of ischaemic stroke.[8,9]

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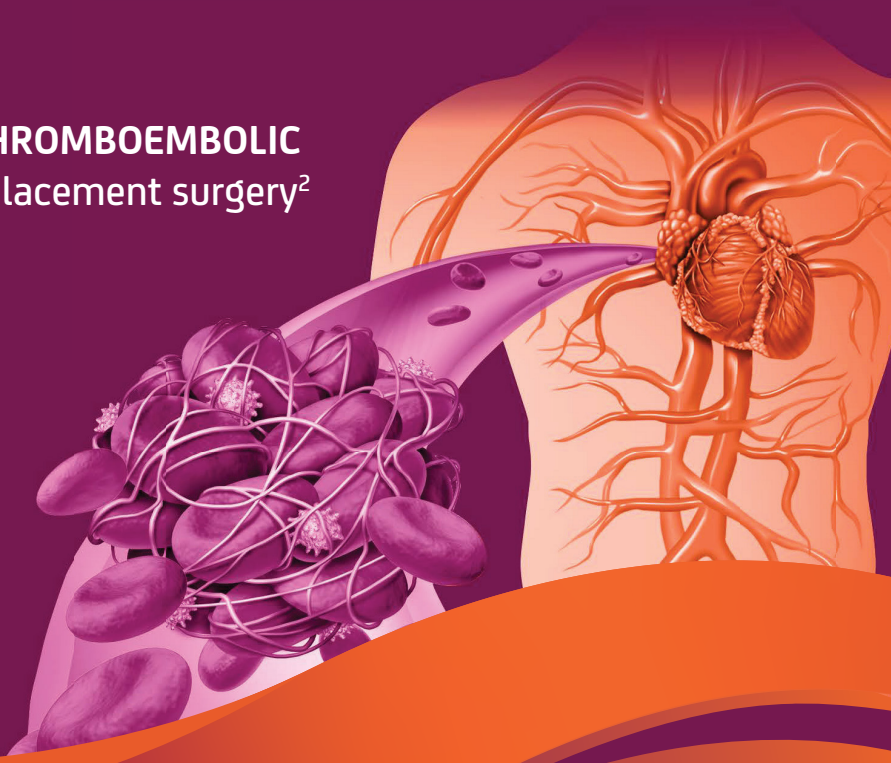

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References: 1. Data on file, IQVIA MIDAS, Patient treatment days prescribed Q2 2022
2. Pfizer Laboratories (Pty) Ltd. ELIQUIS® (apixaban) 2,5 mg and 5 mg Film-coated Tablets. Approved Package Insert – 11 July 2022.

S4 **ELIQUIS®** 2,5MG AND 5MG FILM-COATED TABLETS (REG. NO'S: 45/8.2/0463, 0464). EACH FILM-COATED TABLET CONTAINS EITHER 2,5 MG OR 5 MG APIXABAN.

To report an adverse event, please contact ZAF.AEReporting@pfizer.com. If you wish to contact Pfizer for any other purpose, please use contact details: +2711 320 6000 or 0860 734 937 (SA). Monday-Friday 09h00-17h00.

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2 Haemorrhagic stroke is caused by the rupture of a blood vessel or abnormal vascular structure. Haemorrhagic stroke is further subdivided into intracerebral haemorrhage and subarachnoid haemorrhage. Intracerebral haemorrhage is the most common type of non-traumatic intracranial haemorrhage.[8]

Ischaemic strokes account for 80% of cases, and haemorrhagic strokes account for 20%, but there are regional differences. Data from the Global and regional effects of potentially modifiable risk factors associated with acute stroke in 22 countries (INTERSTROKE): A case-control study found that in Africa, about 66% of strokes were ischaemic and 34% were haemorrhagic, while in high-income countries, about 91% were ischaemic and 9% were haemorrhagic.[8]

A previous stroke significantly elevates the risk of a subsequent stroke with a recurrence rate of 5%–25% in one year and 20%–40% in five years. Strokes due to AFib are associated with very poor outcomes (70%–80% of patients die or become disabled). Therefore, preventing stroke should be considered a global public healthcare priority.[8,9]

How to prevent stroke in patients living with AFib

For decades, warfarin has been the standard treatment for stroke prevention in patients with AFib. However, its use comes with challenges such as regular coagulation monitoring and potential interactions with food and drugs.[1]

In recent years, non-vitamin K antagonist oral anticoagulants (NOACs) have gained approval and recommendation as alternative treatments for stroke prevention in patients living with AFib.[1]

Clinical trials, including the *Randomized Evaluation of Long-Term Anticoagulation Therapy* (RE-LY), *Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation* (ROCKET-AF), *Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation* (ARISTOTLE) study, and *Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction* 48 (ENGAGE AF-TIMI), have demonstrated the efficacy and safety of NOACs.[1,10–13]

The RE-LY study (2009) showed that dabigatran administered at a dose of 150mg, was associated with lower rates of stroke/systemic embolism (SE) but similar rates of major haemorrhage compared to warfarin.[10]

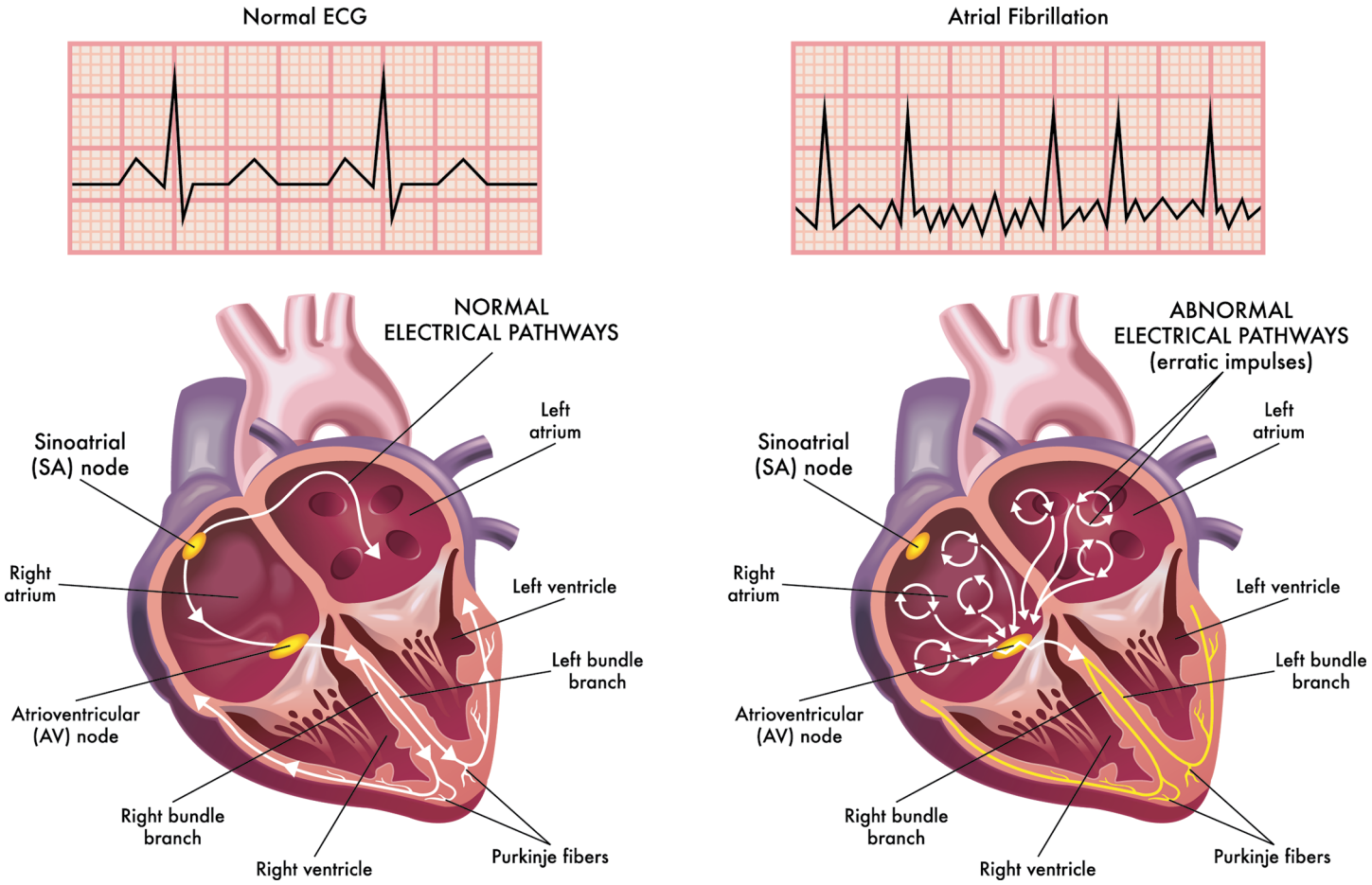
ROCKET-AF (2011) found that rivaroxaban was non-inferior to warfarin for the prevention of stroke/SE. There was no significant between-group difference in the risk of MB, although intracranial and fatal bleeding occurred less frequently in the rivaroxaban group.[11]

ARISTOTLE (2011) reported that apixaban was superior to warfarin in preventing stroke/SE, causing less bleeding, and resulting in lower mortality and ENGAGE AF-TIMI (2013) concluded that both once-daily regimens of edoxaban were non-inferior to warfarin concerning the prevention of stroke/SE and were associated with significantly lower rates of bleeding and death from CV causes.[12]

What about 'real-world' evidence

Guidelines now advocate for the use of NOACs over warfarin in eligible patients, supported by increasing real-world evidence. One of the largest observational analyses to date on NOACs versus warfarin was the *Anticoagulants for Reduction in Stroke: Observational Pooled Analysis on Health Outcomes and Experience of Patients* (ARISTOPHANES) study (2018).[1,13]

ARISTOPHANES compared stroke/SE, and MB among patients living with AFib on NOACs or warfarin. The study used data from 434 046 patients who were included in six matched cohorts: apixaban/warfarin (n=100 977), dabigatran/warfarin (n=36 990), rivaroxaban/warfarin (n=125 068), apixaban/dabigatran (n=37 314), apixaban/



rivaroxaban (n=107 236), and dabigatran/rivaroxaban (n=37 693).[14]

Before matching patients, warfarin patients were found to be the oldest and had the highest baseline risk scores, while apixaban, rivaroxaban, and dabigatran patients followed in that order. After matching, patients were analysed separately for each cohort, making direct comparisons across cohorts inappropriate.[14]

The study revealed that all NOACs were associated with lower rates of stroke/SE when compared to warfarin. Additionally, NOACs were linked to lower rates of haemorrhagic stroke, with apixaban and rivaroxaban patients showing lower rates of ischaemic stroke compared to warfarin.[14]

Regarding MB, both apixaban and dabigatran demonstrated lower rates than warfarin, while rivaroxaban showed a higher rate. Furthermore, all three NOACs were associated with a lower rate of intracranial haemorrhage compared to warfarin. Apixaban was linked to a lower rate of gastrointestinal (GI) bleeding, while rivaroxaban showed a higher rate compared to warfarin.[11]

In the comparison of NOACs to each other, apixaban displayed a lower rate of stroke/SE and MB compared to dabigatran and rivaroxaban. Dabigatran was associated with a lower rate of MB compared to rivaroxaban, but similar rates of stroke/SE.[14]

Subgroup analyses were conducted to assess the effects of age, sex, baseline CHA_2DS_2-VASc score, HAS-BLED score, congestive heart failure, coronary artery disease, peripheral arterial disease, diabetes, renal disease, and prior stroke/SE. The results were generally consistent with the main analysis, with some significant interactions observed.[14]

In the dose subgroup analysis, lower and standard-dose NOAC patients showed consistent results compared to the main analysis, suggesting that dosage variations did not significantly impact the findings. Two sensitivity analyses were performed, and their results aligned with the main analysis, indicating the robustness of the study's findings.[14]

More recently, Deitelzweig *et al* (2022) conducted a meta-analysis, which included 55 studies comparing the real-world effectiveness and safety of NOACs and vitamin K antagonists (VKAs) among patients with non-valvular AFib.[1]

The analysis assessed various outcomes, including all-cause stroke/SE, major bleeding, ischaemic stroke, intracranial haemorrhage, GI bleeding, and all-cause mortality.[1]

The analysis revealed that apixaban, dabigatran, and rivaroxaban were associated with a significantly reduced risk of all-cause stroke/SE compared to VKAs. All NOACs, except rivaroxaban, were found to be associated with a reduced risk of major bleeding.[1,14]

Regarding specific outcomes, treatment with apixaban, dabigatran, and rivaroxaban showed significant associations with a reduced risk of ischaemic stroke, intracranial haemorrhage, and all-cause mortality when compared to VKAs.[1,14]

Edoxaban also demonstrated a reduced risk of these outcomes compared to VKAs, but the credible intervals for this comparison were wide, indicating some uncertainty in the results.[1,14]

Apixaban and edoxaban were associated with a significantly reduced risk of GI bleeding compared to VKAs, whereas dabigatran and rivaroxaban showed no significant differences.[1,14]

Overall, the analysis provides a comprehensive assessment of the impact of NOAC treatment in real-world settings and offers reliable evidence to inform future clinical guidelines for NOACs. The findings are consistent with previous studies on both real-world evidence and randomised controlled trials.[1,14]

Conclusion

Four pivotal randomised controlled trials demonstrated the non-inferiority of apixaban, dabigatran, edoxaban, and rivaroxaban to warfarin for the prevention of stroke/SE. A meta-analysis showed that NOACs reduced the risk of stroke/SE by 19% and all-cause mortality by 10% compared to warfarin.[4]

Adherence to NOAC therapy is generally higher than to warfarin, facilitated by better pharmacokinetics and favourable safety and efficacy profiles. Reduced dose regimens of NOACs are feasible options for patients with severe chronic kidney disease.[4]

Optimising NOAC therapy based on individual patient characteristics is essential to maximise benefits and minimise risks. Overall, NOACs are a compelling treatment option for patients living with AFib, according to the ESC.[4]

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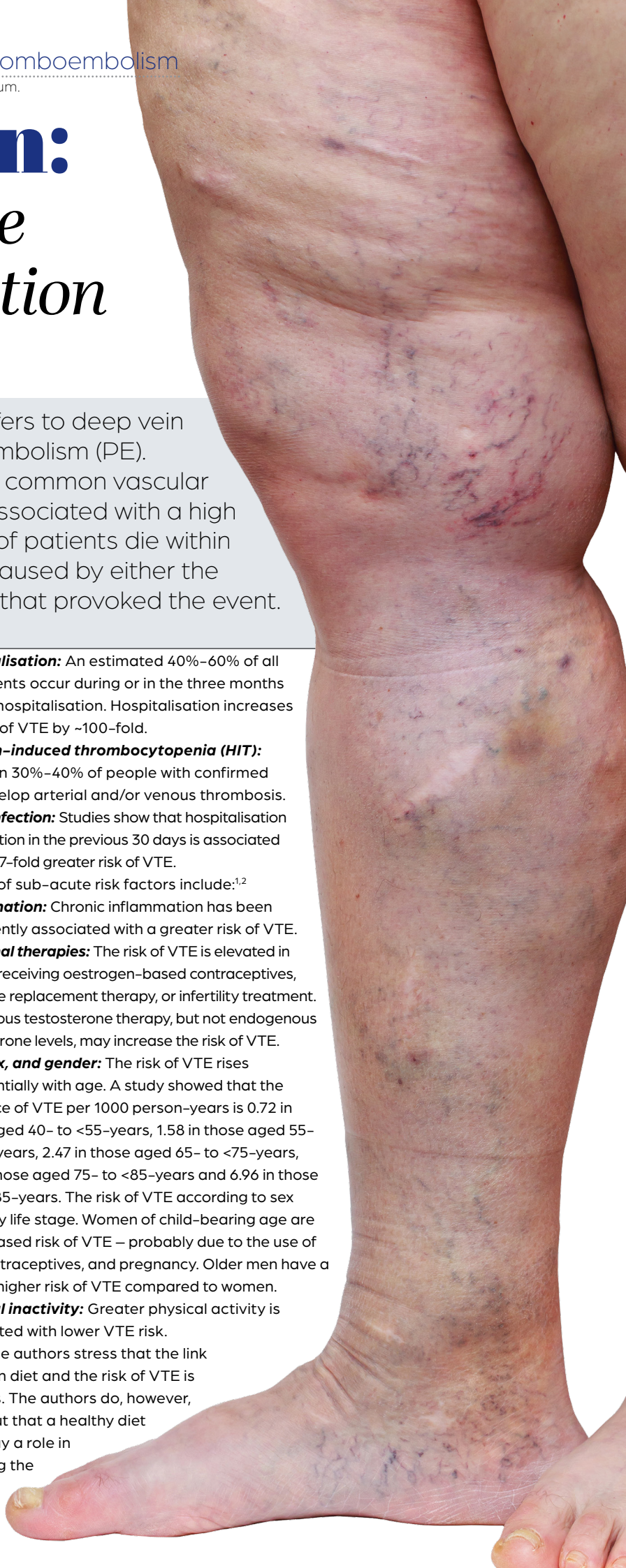
Apixaban: An effective treatment option for VTE



Venous thromboembolism (VTE) refers to deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE ranks among the top five most common vascular diseases in most countries. VTE is associated with a high risk of mortality (an estimated 20% of patients die within one year of diagnosis). Mortality is caused by either the VTE event or the disease/condition that provoked the event. Fortunately, VTE is preventable.[1]

DVT (a blood clot that develops in the deep veins, usually in the lower extremities eg the leg but can also occur in the arms and the mesenteric and cerebral veins), or PE (when a part of the DVT clot breaks off and travels to the lungs) events, are classified as either provoked or unprovoked.[2,3,4]

A provoked DVT or PE occurs in a patient with an acute or transient (resolves after the event) risk factor for VTE (eg major surgery, cancer), while an unprovoked event can occur in patients with no major risk factors. PE has a higher risk of mortality than DVT.[1,4]

VTE risk factors

Examples of acute risk factors of a VTE event include:[1,2]

- ***Surgery:*** Risk factors for VTE after surgery include basal risk factors (eg older age, male sex), comorbid conditions (eg obesity, active cancer, and malnutrition), and postoperative complications (eg pneumonia, blood transfusions, and myocardial infarction).
- ***Bone fracture:*** Risk may be higher with lower-leg, long-bone fractures, trauma-related bone fractures, and operatively treated bone fractures.
- ***Minor injuries:*** Increase the risk of VTE by about five-fold. Certain genetic factors have been associated with an increased risk of VTE including for example: V Leiden variant in the *F5* gene (50-fold), prothrombin G20210A polymorphism [nine-fold], and family history of VTE [12-fold]. The risk of VTE is also higher with more severe injuries, leg injuries, and injuries in the previous four weeks.
- ***Hospitalisation:*** An estimated 40%–60% of all VTE events occur during or in the three months after a hospitalisation. Hospitalisation increases the risk of VTE by ~100-fold.
- ***Heparin-induced thrombocytopenia (HIT):*** Between 30%–40% of people with confirmed HIT develop arterial and/or venous thrombosis.
- ***Acute infection:*** Studies show that hospitalisation for infection in the previous 30 days is associated with a 2.7-fold greater risk of VTE.

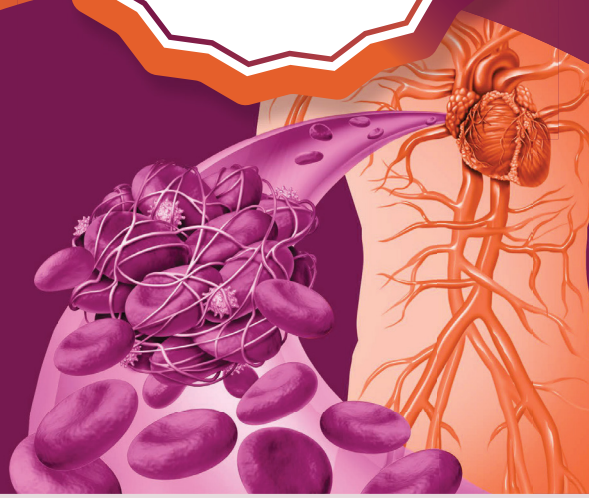
Examples of sub-acute risk factors include:[1,2]

- ***Inflammation:*** Chronic inflammation has been consistently associated with a greater risk of VTE.
- ***Hormonal therapies:*** The risk of VTE is elevated in women receiving oestrogen-based contraceptives, hormone replacement therapy, or infertility treatment. Exogenous testosterone therapy, but not endogenous testosterone levels, may increase the risk of VTE.
- ***Age, sex, and gender:*** The risk of VTE rises exponentially with age. A study showed that the incidence of VTE per 1000 person-years is 0.72 in those aged 40- to <55-years, 1.58 in those aged 55- to <65-years, 2.47 in those aged 65- to <75-years, 3.12 in those aged 75- to <85-years and 6.96 in those aged ≥85-years. The risk of VTE according to sex varies by life stage. Women of child-bearing age are at increased risk of VTE – probably due to the use of oral contraceptives, and pregnancy. Older men have a slightly higher risk of VTE compared to women.
- ***Physical inactivity:*** Greater physical activity is associated with lower VTE risk.
- ***Diet:*** The authors stress that the link between diet and the risk of VTE is tenuous. The authors do, however, point out that a healthy diet may play a role in reducing the risk of VTE.

Eliquis® apixaban

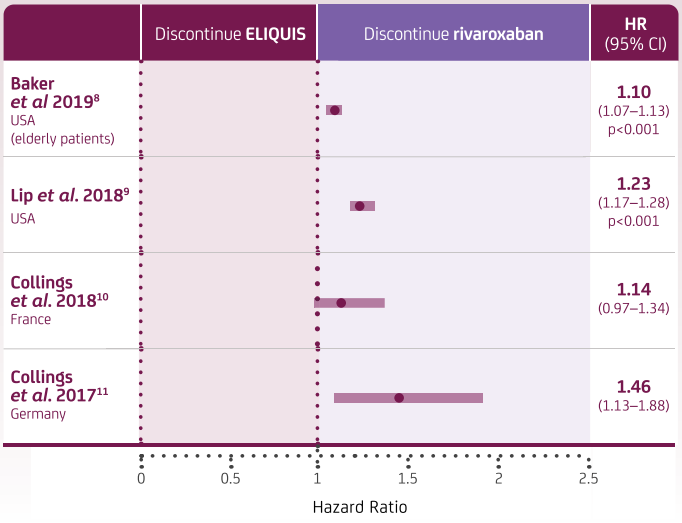
2.5mg, 5mg

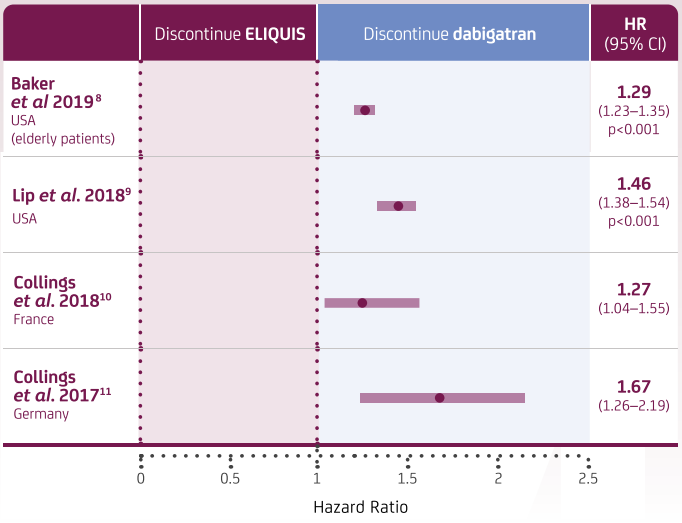
- Adequate adherence and persistence with **NOACs for stroke prevention is essential.**[2]
- **Adherence with NOACS of above 90%** gave optimal stroke prevention.[2]



More of your NVAF patients stay on ELIQUIS® in clinical trials and real-world studies.[3-7] A similar or higher proportion of patients maintained continuous treatment with twice-daily ELIQUIS® vs. other NOACs across real-world studies.[8-17]

SELECTED REAL-WORLD PERSISTENCE ANALYSES[8-11†]





There are no head-to-head RCTs comparing the NOACs. Comparisons cannot be made between individual NOACs based on these data.

† These studies presented were selected on the basis that they were analysed against apixaban as the reference NOAC

Choose Eliquis® for the Prevention of Stroke and Systemic Embolism in your patients with Non-valvular Atrial Fibrillation.[18]

NVAF: nonvalvular atrial fibrillation; **NOAC:** new oral anticoagulants; **RCT:** randomised controlled clinical trials

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To report an adverse event, please contact ZAF.AEReporting@pfizer.com. If you wish to contact Pfizer for any other purpose, please use contact details: +2711 320 6000 or 0860 734 937 (SA). Monday-Friday 09h00-17h00.

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- ***Tobacco smoking:*** May increase the risk of VTE because it promotes coagulability and chronic inflammation. A meta-analysis showed that the adjusted hazard ratios (HR) for the association between current smoking and provoked or unprovoked VTE events were 1.36 and 1.08.
- ***Obesity:*** High body mass index (BMI) has been consistently associated with an elevated risk of VTE. A study showed the risk of VTE was 1.58 for BMI 25kg/m^2–≤30kg/m^2, 2.10 for BMI 30kg/m^2 to ≤35kg/m^2, and 3.09 for BMI ≥35kg/m^2.

Examples of acquired risk factors include:[1]

- ***Cancer:*** The annual incidence of VTE in patients living with cancer ranges from 0.5% to 20% depending on the cancer type and treatments.
- ***Autoimmune diseases:*** Antiphospholipid syndrome predisposes individuals to VTE.

Other factors that may provoke a VTE event include: Comorbidities (eg kidney disease, heart failure, and atrial fibrillation), immobility, adverse environmental conditions (such as air travel), and a previous VTE.[1]

Signs and symptoms of DVT and PE

Up to 50% of patients with DVT lack specific signs or symptoms. Signs of acute lower extremity DVT include pain, swelling, tenderness, and cyanosis. However, these symptoms are non-specific and can be misdiagnosed as other lower extremity disorders like lymphedema or cellulitis. The sensitivity and specificity of clinical signs and symptoms are inconsistent, making it difficult to accurately diagnose or exclude DVT based on them.[3]

The most common symptoms of PE include dyspnoea, pleuritic chest pain, cough, haemoptysis, presyncope, or syncope. Dyspnoea can range from acute and severe in central PE, to mild and transient in small peripheral PE. Chest pain is frequent and is often caused by pleural irritation due to pulmonary infarction.[5]

Less common presentations include arrhythmias, syncope, and haemodynamic collapse. Haemodynamic instability indicates severe PE with reduced haemodynamic reserve. It's important to note that some patients with a large PE may be asymptomatic or have mild symptoms, and PE can be discovered incidentally during diagnostic workup for other conditions.[5]

Can VTE be prevented?

Yes, it can. Strategies for the prevention of VTE are classified into three categories: Primordial, primary, and secondary prevention.[1]

1. ***Primordial prevention:*** This approach focuses on preventing the development of risk factors for VTE in healthy individuals. Lifestyle interventions, such as promoting physical activity, maintaining a healthy diet, and smoking cessation, can contribute to reducing the risk of VTE. Even for individuals with genetic risk factors, adopting a healthy lifestyle can help mitigate the increased risk.
2. ***Primary prevention:*** Involves specific interventions for individuals at risk of VTE. Common interventions include pharmacological prophylaxis – especially for hospitalised patients or those living with cancer.
3. ***Secondary prevention:*** Aimed at preventing recurrent VTE events in patients with a history of VTE. Anticoagulation therapy is the traditional approach for secondary prevention (see below), as patients with a previous VTE event are at a higher risk of recurrence. Decisions regarding secondary prevention should be made throughout a patient's life course, especially during periods of increased VTE risk, such as pregnancy, use of hormone therapy, hospitalisation, or surgery.

Improving awareness of VTE is crucial for early diagnosis and appropriate management. Currently, awareness of VTE is generally low in the general population, and even among individuals at high risk. Educating both the general public and healthcare professionals can lead to better recognition and adherence to guideline-based care.[1]

Strategies for the prevention of VTE are classified into three categories: Primordial, primary, and secondary

What is the cornerstone of VTE treatment?

Conventional VTE therapies comprise a parenteral anticoagulant (eg unfractionated heparin or low-molecular-weight heparin [LMWH]) and/or a vitamin K antagonist (VKA, eg warfarin).[6]

However, since the introduction of direct anticoagulants – also known as non-vitamin K antagonists oral anticoagulants (NOACs) – guidelines recommend these agents over conventional therapies. Approved NOACs include dabigatran (a thrombin inhibitor), as well as rivaroxaban, apixaban, and edoxaban (factor Xa inhibitors).[6]

Guidelines recommend anticoagulation therapy for at least three to six months in all cases. However, patients at high risk of recurrence (patients living with cancer, inflammatory diseases, or serious acquired or inherited thrombophilic alterations, as well as those at risk of repeated VTE events, or who experienced a first VTE event are at risk of experiencing a subsequent event five years after an initial diagnosis) need maintenance therapy. In these cases, indefinite anticoagulant treatment is recommended.[7]

In patients with unprovoked VTE, guidelines suggest extended (without a predetermined stop date) anticoagulation treatment – provided the risk of bleeding associated with anticoagulation, is not high.[7]

At the end of the maintenance period, guidelines recommend that all patients with an acute VTE event should undergo risk assessment. Based on the outcomes, clinicians can opt to:[7]

- Interrupt any specific pharmacological treatment
- Continue with extended anticoagulation using the same or another anticoagulant drug, at standard or reduced dosage
- Replace the anticoagulant in use with an alternative antithrombotic drug.

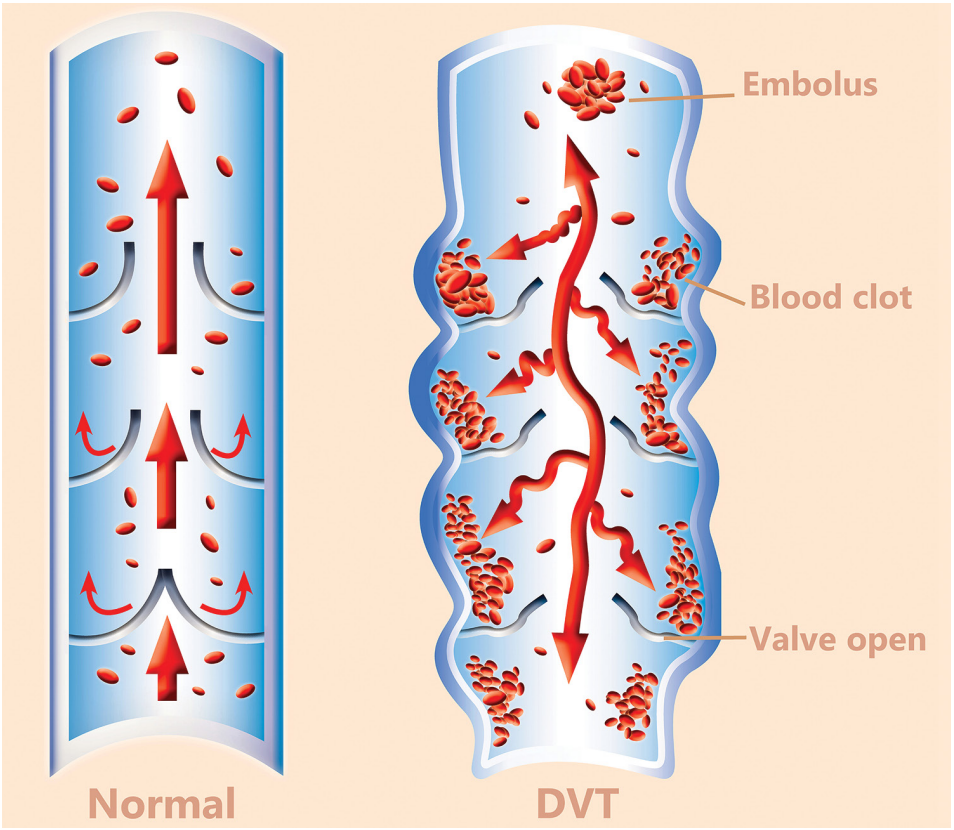
It should be noted that estimating individual risks are not always easy. A number of factors can influence clinical decision-making including patient preference, concurrent diseases and treatments, healthcare system support, and availability of potentially effective treatments alternative to anticoagulation.[7]

What can we learn from real-world data?

Real-world data indicate that not all NOACs are created equal. For example, Dawwas *et al* compared the safety and effectiveness of apixaban and rivaroxaban – both of which are increasingly being used to replace warfarin.[8]

A number of studies have shown that NOACs have fewer drug-drug interactions, and lower bleeding rates compared to warfarin, and do not require routine laboratory monitoring.[8]

Although several small observational studies have compared apixaban and rivaroxaban, no head-to-head studies have been conducted until recently. In 2022, Dawwas *et al*, set about conducting a real-world, head-to-head study comparing apixaban and rivaroxaban.[8]



The study compared data from 49 900 adult participants with VTE, of which 18 618 respectively, were newly prescribed to either apixaban or rivaroxaban. The median follow-up was 102 days. The primary effectiveness endpoint was recurrent VTE (a composite of DVT and PE) and the primary safety endpoint was a composite of gastrointestinal (GI) and intracranial (IC) bleeding.[8]

Compared with rivaroxaban users, apixaban users were older (70- vs 66-years) and had a higher prevalence of chronic kidney disease (41% vs 28%), diabetes (35% vs 27%), heart failure (27% vs 17%), and hypertension (76% vs 65%).[8]

In terms of rates of recurrent VTE, 8.9 events per 100 person-years VTE events occurred among apixaban study participants, compared to 11.4 events per 100 person-years in the rivaroxaban group. The absolute reduction in the probability of recurrent VTE with apixaban compared with rivaroxaban was 0.006 within two months, and 0.011 within six months of treatment initiation. Results were consistent for apixaban (vs rivaroxaban) for DVT and PE.[8]

Results from the safety analysis showed that in the matched sample, GI and IC bleeding events among apixaban users were 7.2 events per 100 person-years, compared to 11 events per 100 person-years) (HR 0.60) in the rivaroxaban group. The absolute reduction in the probability of GI and IC bleeding with apixaban compared with rivaroxaban was 0.011 within two months and 0.015 within six months of treatment initiation. Results were consistent for apixaban (vs rivaroxaban) for GI (HR 0.60) and IC (HR 0.54) bleeding.[8]

The authors concluded that in this comparative effectiveness and safety study using real-world data, adults with VTE who initiated apixaban had a lower rate of recurrent VTE, as well as GI and IC bleeding events compared to rivaroxaban. These findings suggest that apixaban is more effective and safer compared to rivaroxaban. These findings may provide guidance to clinicians and patients regarding the selection of an anticoagulant for the treatment of VTE.[8]

Conclusion

VTE is among the top five most common vascular diseases in most countries and is associated with a high risk of mortality. Strategies for preventing VTE can be divided into primordial, primary, and secondary prevention and are aimed at targeting risk factors and introducing specific interventions for at-risk patients.

NOACs have emerged as a preferred choice for VTE treatment over warfarin due to their fixed dosing, fewer drug interactions, and lower bleeding rates. A head-to-head study comparing apixaban with rivaroxaban, found that apixaban users had a lower rate of recurrent VTE as well as GI and IC bleeding events compared to rivaroxaban users. This suggests that apixaban may have superior effectiveness and safety in VTE treatment, providing valuable guidance for clinicians and patients in selecting the appropriate anticoagulant.

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Scan for the quiz

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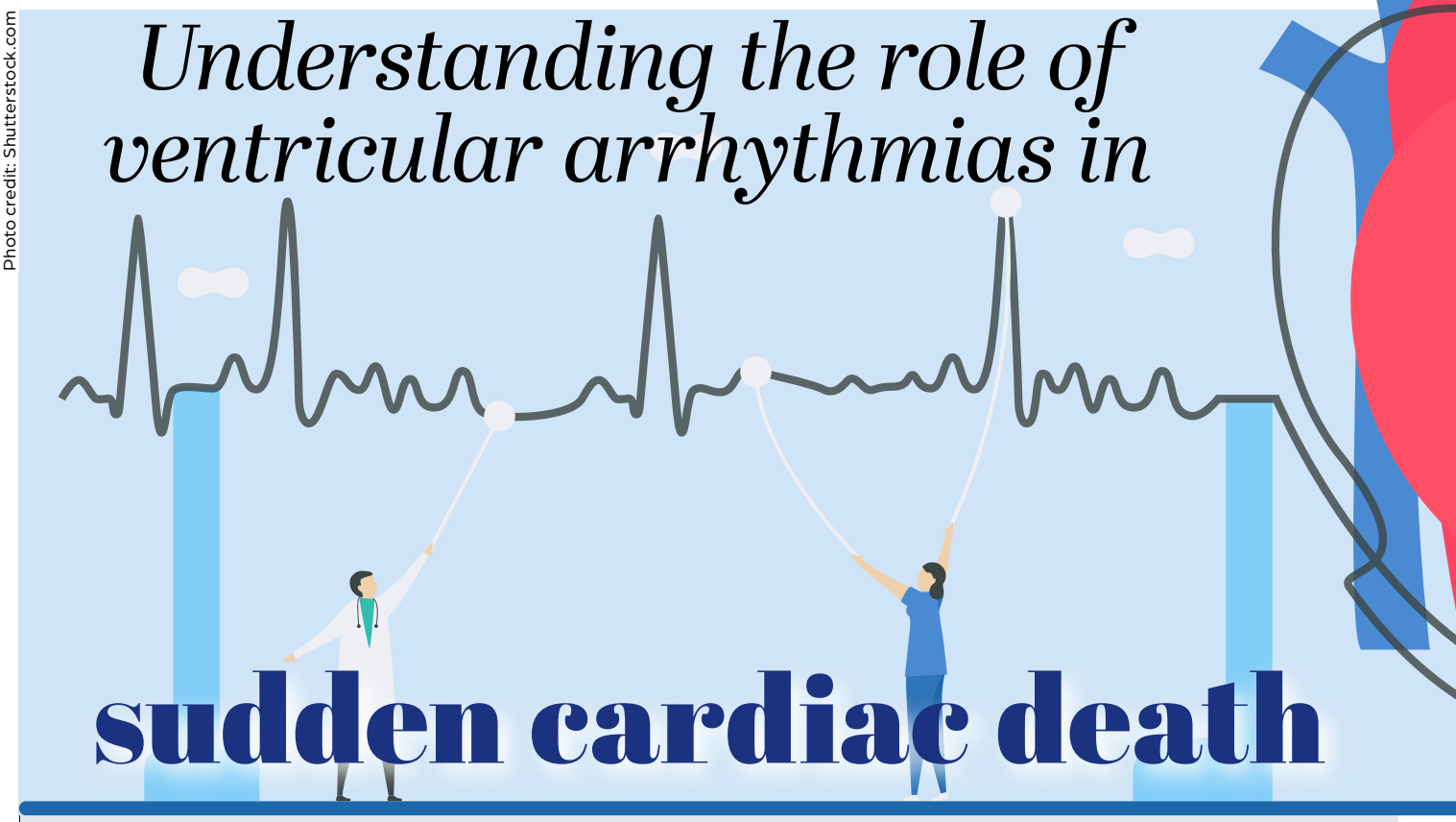
Understanding the role of ventricular arrhythmias in sudden cardiac death



Did you know that ~50% of all cardiovascular (CV) deaths are attributed to sudden cardiac death (SCD)? SCD is defined as a presumed natural death related to the heart, occurring within one hour of a witnessed onset, or within 24 hours of last being seen alive if unwitnessed. Unfortunately, in many instances SCD is the first sign of an underlying and potentially fatal CV disease (CVD).[1]

According to the European Society of Cardiology (ESC), cardiac arrhythmias – most notably ventricular arrythmias (VAs) – are the main culprits responsible for SCD, leading to cessation of the heart's contractions and subsequent deprivation of blood supply to critical organs such as the brain. The immediate outcome is a loss of consciousness, and should the arrhythmia persist for more than five minutes, the patient will die.[1,2]

Patients mostly affected by SCD include those with underlying CVDs (eg coronary artery disease [CAD] is implicated in 75%–80% of cases with or without myocardial infarction [MI], others include dilated or hypertrophic myocardiopathy, and arrhythmogenic right ventricular dysplasia). Furthermore, patients with a history of VAs or those who exhibit severely impaired ventricular function, are at an even highest risk of SCD.[1,2,3]

Several other factors are also associated with an increased SCD risk, including age (mid-30s to mid-40s) gender (males have the highest risk), cigarette smoking, as well as comorbidities such as hypertension, diabetes, and obesity.[3]

Some studies also show that socio-economic status is a risk factor. These studies found that the incidence of SCD is higher in patients in socio-economically disadvantaged communities as opposed to their more affluent counterparts.[3]

Psychological factors that play a role include social isolation, stress, and considerable life event changes. Studies show that patients who suffered a SCD episode experienced life-changing events six months prior to the incident.[3]

Furthermore, cautions the ESC, while routine physical activity is advantageous for overall health and CV well-being, engaging in sports, especially at intense levels, has been linked to SCD either during or shortly after exercise in at risk patients.[1]

Studies indicate that the majority of SCD incidents related to sports occur in a recreational context rather than in competitive settings. This trend is notably prominent among middle-aged male participants.[1]

Electrical diseases

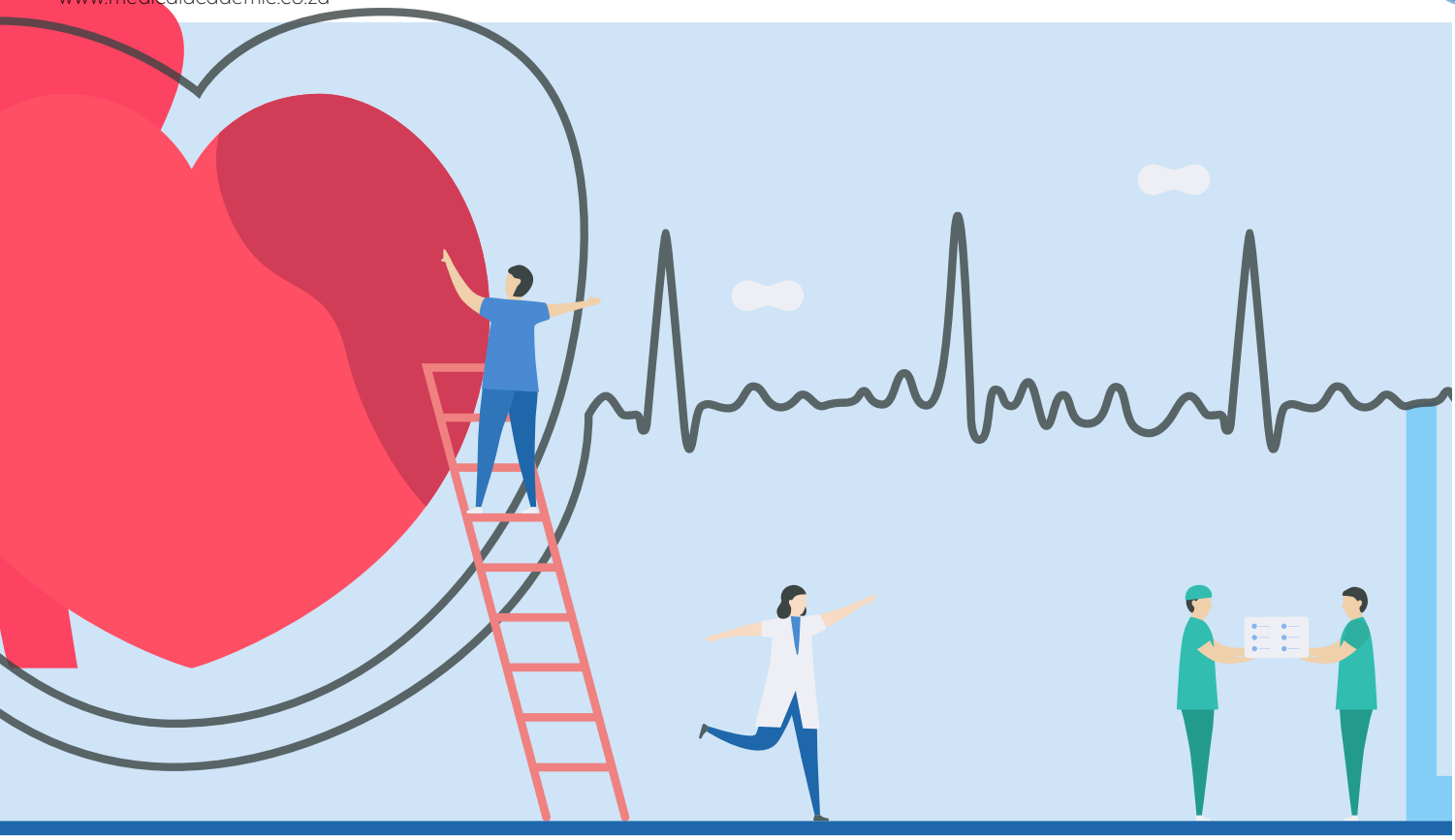
Although VAs is implicated in the majority of cases, a subset of patients faces the risk of SCD despite evidence of CVD. Patients in this subgroup suffer from so-called 'electrical diseases', according to Brugada.[2]

Over recent years, several conditions falling under this umbrella have been identified, including long QT syndrome (LQTS), Brugada syndrome, short QT syndrome (SQTS), and catecholaminergic polymorphic ventricular tachycardia (CPVT).[2]

These conditions are primarily familial, rooted in genetic defects affecting certain electrical channels within the heart. Across all these disorders, the ultimate consequence is the onset of fatal VAs, such as monomorphic VT or ventricular fibrillation (VF), leading to SCD.[2]

VT involves ≥3 consecutive ventricular beats with a rate ≥100 beats per minute, distinct from atrial and atrioventricular conduction. Monomorphic VT maintains consistent QRS morphology, while polymorphic VT exhibits changing morphologies. *Torsades de Pointes* is a polymorphic VT with spiral QRS complexes in QT prolongation.[1]

Other types of VT include non-sustained VT, which persists for three beats to 30 seconds and sustained VT, which lasts for at least 30 seconds and bidirectional VT displays alternating frontal QRS axes. Incessant VT persists despite repeated interventions. VF presents chaotic undulating rhythms without discrete QRS complexes.[1]



VAs can also manifest as premature ventricular complexes (PVC). PVC is characterised by abnormal QRS complexes and broad T-waves. Unifocal PVCs exhibit a singular QRS morphology, while multifocal PVCs present diverse morphologies. Short-coupled PVCs disrupt preceding T-waves.[1]

How are ventricular arrhythmias treated?

According to the ESC guidelines, ~50% of SCD cases stem from reversible factors, although pinpointing the exact cause is often challenging. In patients who have experienced syncope following a previous ST-elevation MI, programmed electrical stimulation (PES) is recommended when the cause of syncope remains unexplained after non-invasive evaluation.[1]

For patients undergoing an acute phase of acute coronary syndrome with recurrent polymorphic VT or VF, intravenous (IV) amiodarone treatment is advised.[1]

In cases of CAD where implantable cardioverter-defibrillator (ICD) placement is eligible, catheter ablation may be considered just before or after ICD implantation to reduce subsequent VT burden and ICD shocks.[1]

For patients with PVC-induced cardiomyopathy, catheter ablation is recommended. In dilated cardiomyopathy or non-ischaemic dilated cardiomyopathy, ICD implantation is recommended for those with symptomatic heart failure (New York Heart Association class II–III) and left ventricular ejection fraction (LVEF) ≤35% after ≥3 months of optimal medical therapy.[1]

Additionally, catheter ablation in specialised centres should be considered for patients with recurrent, symptomatic sustained monomorphic VT or ICD shocks for symptomatic monomorphic VT, in whom antiarrhythmic drugs (AADs) are ineffective, contraindicated, or not tolerated.[1]

For arrhythmogenic right ventricular cardiomyopathy patients with arrhythmic syncope, ICD implantation can be considered, and the same recommendation applies to those with severe right or left ventricular systolic dysfunction.[1]

In inflammatory diseases such as myocarditis and cardiac sarcoidosis, ICD implantation is recommended for haemodynamically not-tolerated symptomatic monomorphic VT in the chronic phase of myocarditis, and it is also recommended for patients with cardiac sarcoidosis who have an LVEF ≤35%.[1]

ICD implantation is further recommended for cardiac sarcoidosis patients with documented sustained VT or aborted cardiac arrest. In Chagas' cardiomyopathy, where symptomatic VT is unresponsive to AADs, ICD implantation may be considered.[1]

For congenital heart disease (CHD) patients post-repair of tetralogy of Fallot without arrhythmia symptoms, electrophysiologic evaluation, including PES, may be considered.[1]

In CHD patients with recurrent, symptomatic monomorphic VT or ICD shocks not manageable by medical therapy or ICD reprogramming, catheter ablation performed in specialised centres is recommended.[1]

For primary electrical diseases and selected populations, ICD implantation is recommended in LQTS patients who are symptomatic while receiving beta-blockers and genotype-specific therapies.[1]

ICD implantation should be considered in CPVT patients experiencing arrhythmic syncope and/or documented bidirectional/PVT while on the highest tolerated beta blocker dose and on flecainide.[1]

Pre-participation CV evaluation of competitive athletes is recommended. Catheter ablation of triggering PVCs and/or right ventricular outflow tract epicardial substrate should be considered in patients living with Brugada syndrome with recurrent appropriate ICD shocks refractory to drug therapy.[1]

Lastly, left cardiac sympathetic denervation should be considered in CPVT patients when the combination of beta blockers and flecainide at therapeutic dosage is either not effective, not tolerated, or contraindicated.[1]

Are ADDs still relevant in the era of ICDs?

Despite ESC recommendations, some researchers question whether AADs are still relevant in the treatment of VAs to prevent SCD in the ICD era. Currently four classes of AADs are approved for the treatment of VAs (see below).[4]

According to Zaki *et al*, AAD prophylaxis alone is not justified for the prevention of SCD if an ICD is an option. However, given AADs anti-arrhythmic efficacy, it may have

an adjunctive role in ICD recipients who have frequent VAs triggering by ICD discharges.[3]

The team performed a meta-analysis comparing the efficacy of amiodarone, the most evidence-based pharmacotherapy for recurrent VAs, versus ICD to reduce SCD rates. Amiodarone is particularly effective in maintaining long-term sinus rhythm.[5]

Amiodarone primarily blocks delayed rectifier potassium channels, demonstrating effectiveness in treating VAs. As an iodinated benzofuran derivative, its unpredictable pharmacokinetics make it a versatile class III agent, influencing refractoriness in cardiac regions and incorporates the properties of all four AAD classes.[4,5]

Furthermore, amiodarone – especially in conjunction with beta blockers – have been shown to reduce arrhythmic death rates in heart failure patients. Amiodarone also serves as a crucial adjuvant for decreasing shocks in ICD recipients.[5]

In their meta-analysis, Zaki *et al* found that ICDs were more effective in the reduction of SCD rates, with an SCD rate of 5.97% observed in the ICD group compared with an SCD rate of 11.81% observed in the amiodarone group. The results also show that ICDs were more effective in reducing all-cause mortality.[3]

The team concluded there is evidence that amiodarone can be used as an adjuvant treatment option, especially for patients who are not eligible for ICD treatment and those who face more adverse events. Evidence has also shown that using amiodarone with ICD treatment significantly improves survival rates compared to ICD treatment only.[3]

What about other AAD classes and agents?

1. *Sodium channel blockers*

Class I AADs impact the cardiac electrical system by blocking sodium channels, with subclasses IA, IB, and IC. They exhibit use-dependent behaviour, becoming more potent at higher heart rates.[4]

Class IA drugs, like procainamide, prolong action potential duration and effective refractory period, decreasing automaticity. Procainamide, in particular, has shown efficacy in terminating VT. Quinidine, a class IA drug, has been used as salvage therapy for recurrent VT in structural heart disease.[4]

Class IB drugs, including lidocaine and mexiletine, reduce maximal depolarisation velocity, shortening action potential and refractory period. Lidocaine is commonly used in acute inpatient treatment of VAs but lacks strong evidence supporting its efficacy.[4]

Mexiletine is used as an alternative or adjunctive therapy, especially in patients with toxicity to Class III agents. It has shown efficacy in congenital LQTS type 3.[4]

Class IC drugs, like flecainide and propafenone, significantly reduce action potential conduction velocity. These drugs are potent but are generally avoided in structural heart disease due to increased mortality. They may be considered in specific cases, such as CPVT or as a secondary option in LQTS treatment.[4]

2. *Beta blockers*

Beta blockers, crucial in heart failure therapy, exhibit anti-arrhythmic effects by blunting sympathetic activity. They reduce phase 4 depolarisation, diminishing automaticity and conduction velocity.[4]

Notably used post-acute MI, beta blockers, like propranolol and carvedilol, reduce cardiac death and VAs. Though large ICD trials revealed no impact on mortality, studies emphasise morbidity reduction.[4]

Beta blockers, especially when combined with amiodarone, significantly decrease the need for ICD therapies, supporting their role in adjunct therapy for secondary prevention of VAs in ischaemic cardiomyopathy.[4]

In specialised cases, beta blockers play a pivotal role. In an acute electrical storm, they effectively reduce intensive care unit (ICU) days, shocks, and overall mortality. Non-selective beta blockers, particularly propranolol, outperform selective counterparts, decreasing VA incidence and ICU admission time. In CPVT, nadolol is recommended for VT prevention.[4]

In LQTS, beta blockers, notably for LQTS1/LQTS2, historically reduce syncopal events, showing modern benefits like shortened QT intervals at faster rates. Despite being first-line therapy for LQTS3, support is limited. Overall, beta blockers play a vital role in managing various arrhythmias with evidence-based effectiveness.[4]

3. *Potassium channel blockers*

Dronedarone, a non-iodinated derivative of amiodarone, shares a similar mechanism of action but with lower rates of thyroid toxicity. It has shown efficacy in managing atrial fibrillation, with limited data on its effectiveness in VAs.[4]

Dofetilide selectively blocks delayed outward rectifying potassium current, demonstrating efficacy in atrial tachyarrhythmias, but its utility in VAs is less understood.[4]

Sotalol, a racemic mixture with both class II and class III effects, has demonstrated efficacy in suppressing ventricular ectopy and reducing inducible VT. However, it requires careful monitoring due to its association with *torsades de pointes*.[4]

4. *Calcium channel blockers*

Verapamil and diltiazem, non-dihydropyridine calcium channel antagonists, primarily affect the atrioventricular-node by blocking slow inward calcium current, prolonging the effective refractory period with minimal impact on atrial/ventricular myocytes or the His–Purkinje system.[4]

While effective in terminating and controlling ventricular rates in supraventricular tachycardias, their utility in VT is limited, as seen in early studies. However, a unique form of VT, idiopathic left VT, with a macro-re-entry circuit, responds to verapamil.[4]

Calcium channel blockers also serve as adjunctive therapy in CPVT and are first-line agents for ILVT, but show limited utility in common forms of VT.[4]

Conclusion

A comprehensive understanding of VAs is crucial in addressing the leading causes of SCD. The intricate relationship between CVDs, electrical disorders, and various risk factors underscores the importance of tailored interventions.

The guidelines provided by the ESC serve as a valuable roadmap for healthcare professionals, emphasising the significance of reversible factors, AADs, and targeted procedures.

While ICDs exhibit superior efficacy in reducing SCD rates, adjunctive treatments such as amiodarone showcase potential benefits, especially in cases where ICD eligibility is limited.

The nuanced approach involving different classes of AADs and their respective roles in managing VAs further highlights the dynamic landscape of treatment modalities. SF

References available in the online issue

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Decoding epilepsy: *Syndromes, age of onset and seizure types*

International Epilepsy Day, which will be commemorated on 12 February this year, is an annual awareness-raising initiative organised by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy. In the first segment of our two-part series on epilepsy, we provide a nutshell overview of the new ILAE classification of epilepsy syndromes. In the second part, we look at the management of adult patients living with epilepsy.

In 2017, the ILAE updated its definitions for epilepsy syndromes, categorising them into three groups: Syndromes with onset in neonates and infants (up to two-years), syndromes beginning in childhood, and syndromes that may commence at a variable age, encompassing both paediatric and adult patients.[1,2]

Typically, an epilepsy syndrome involves common seizure types, electroencephalogram (EEG) patterns, and imaging features that tend to manifest collectively.[2]

This often includes age-dependent characteristics such as the age of onset and remission (if applicable), potential seizure triggers, diurnal variations, occasional prognosis considerations, and notable comorbidities like intellectual and psychiatric disorders.[2]

The incidence of epilepsy reaches its highest rates (>60 per 100 000) in children <5 years old, and those aged ≥65 years. Children frequently experience higher rates of drug resistance, mortality, and up to 50% exhibit global developmental delays two years after presentation. Comorbidities are also more prevalent among those with drug-resistant seizures and those facing a high seizure burden.[2]

Definitions explained

Syndromes with onset in neonates and infants

The ILAE classifies epilepsy syndromes with onset in neonates and infants into two primary groups:[2]

1. Self-limited epilepsy syndromes

- ***Self-limited (familial) neonatal epilepsy (SeLNE):*** Has an incidence of ~5.3 per 100 000 live births. Share clinical and genetic characteristics with self-limited familial neonatal epilepsy (SeLFNIE) but have some differences based on family history. Onset is typically between days two and seven and seizures exhibit focal tonic or clonic features. SeLNE usually resolves by six months. Anti-seizure medication (ASM) can often be discontined within weeks. The infant's development is normal, although some may experience later-life seizures. Seizure clusters may manifest over hours or days, with normal behaviour between events and an unremarkable clinical examination.
- ***Self-limited familial neonatal-infantile epilepsy:*** Caused by dominantly inherited SCN2A or rare potassium voltage-gated channel subfamily Q member 2 pathogenic variants. Should be distinguished from SeLNE or self-limited (familial) infantile epilepsy (SeLIE) based on a documented family history of neonatal or infantile epilepsy onset. Onset is between day two and seven months, featuring focal clonic or tonic seizures in clusters. Typically resolving by 12 to 24 months, SeLFNIE exhibits equal gender prevalence with unremarkable perinatal and developmental histories. Seizures vary in frequency and duration but can be controlled with ASM.
- ***Self-limited (familial) infantile epilepsy:*** Previously known as benign familial infantile seizures. Has an incidence of ~14.2 per 100 000 live births, representing 7%–9% of epilepsies starting <2-years. Onset occurs between three and 20 months. Initially frequent, seizures often remit within a year, though untreated cases may persist. Antenatal, birth, and neonatal history are typically normal, but there is a rare possibility of epilepsy persisting into later life.
- ***Genetic epilepsy with febrile seizures plus (GEFS+):*** Has an unknown incidence. It's an autosomal dominant familial epilepsy spectrum, involving diverse seizure types. While febrile seizures are common, not all affected family members exhibit them. GEFS+ includes myoclonic atonic seizures, Dravet syndrome, genetic generalised epilepsy, and focal epilepsies within families. In the specific febrile seizures plus (FS+) phenotype, seizures may commence before six months, persist beyond six years, and evolve to afebrile seizures. Prolonged focal clonic seizures <15 months suggest Dravet syndrome. Neurological examination and cognition are usually normal. FS+ seizures are typically responsive to ASM.
- ***Myoclonic epilepsy in infancy:*** Is rare, constituting <0.8% of cases. Onset is between four months and three years, peaking at six to 18 months, with a male predominance (~2:1). Seizures, triggered by sudden noise or startle, manifest as myoclonic jerks. The majority remit within six months to five years, and most children can discontinue ASM. Myoclonic seizures involve the head and upper arms, occurring in clusters, with ~30% of cases having reflex-induced seizures triggered by noise or touch. Febrile seizures may precede or follow myoclonic seizures. Developmental outcomes are mostly normal in the long term.

2. Developmental and epileptic encephalopathies (DEEs)

- ***Early infantile developmental and DEE:*** Incidence is ~10 per 100 000 live births, manifests within the first three months with drug-resistant seizures. It includes varied seizure types and is associated with comorbid movement disorders.
- ***Epilepsy of infancy with migrating focal seizures:*** A rare developmental and epileptic encephalopathy (EE), with an estimated prevalence of ~0.11/100 000 live births. Marked by drug-resistant focal seizures in the first year, it often migrates across cortical regions within a seizure. Seizures are prolonged, leading to episodes of *status epilepticus*, and prognosis is poor.
- ***Infantile epileptic spasms syndrome:*** Has an incidence of ~30 per 100 000 live births and includes West syndrome and infants with epileptic spasms not meeting all West syndrome criteria. Onset occurs between one and 24 months, often evolving from early-onset epilepsies, and prognosis varies.
- ***Dravet syndrome:*** Has an incidence of ~6.5 per 100 000 live births, typically begins between three and nine months. It involves prolonged febrile and afebrile seizures, leading to cognitive and behavioural impairments. Sodium channel-blocking drugs exacerbate seizures, aiding in diagnosis.

Syndromes beginning in childhood

Childhood epilepsies include three primary groups:[3,4]

1. *Self-limited focal epilepsies*

Focal epilepsies with onset during childhood are often self-limited and usually of unknown aetiology. Two groups of syndromes are recognised based on long term prognosis.[3]

Group 1

- ***Self-limited epilepsy with centrotemporal spikes (SeLECTS):*** Accounts for ~6%-7% of cases. Onset typically occurs between four and 10 years, with focal seizures involving clonic or tonic activity of the throat, tongue, and lower face. Characterised by a positive family history, distinctive EEG features, and favourable outcomes, SeLECTS often remits by puberty.
- ***Self-limited epilepsy with autonomic seizures:*** Accounts for ~5% of cases, and manifests with focal autonomic seizures triggered by sleep. Despite prolonged seizures, the prognosis is generally favourable, with remission observed within a few years from onset.

Group 2

- ***Childhood occipital visual epilepsy (COVE):*** Onset is around eight to nine years and involves sensory visual phenomena during wakefulness. Seizures are often responsive to ASM, and remission occurs in 50%-80% of patients by puberty, with normal development usually maintained.
- ***Photosensitive occipital lobe epilepsy (POLE):*** A rare syndrome accounting for ~0.7% of cases. POLE manifests with photic-induced focal seizures involving the occipital lobe. Prognosis varies, with some patients experiencing only a few seizures, while others have ongoing photic-induced seizures.

An epilepsy syndrome involves common seizure types, EEG patterns and imaging features

2. *Genetic generalised epilepsy syndromes of childhood*

Genetic aetiology underlies all childhood-onset generalised epilepsy syndromes, characterised by complex inheritance involving polygenic factors, potentially influenced by environmental elements. Syndromes include:[3,4]

- ***Childhood absence epilepsy (CAE):*** Accounts for ~18% of school-aged epilepsy, with an incidence of 6.3-8 per 100 000 per year. Typically affects otherwise healthy children. Children present with daily absence seizures (2.5-4Hz generalised spike-wave at onset), often provoked by hyperventilation. Onset is between four and 10 years and affects more girls (60%-75%). CAE remits in 60% of patients by early adolescence, with potential evolution into other syndromes. Seizures involve staring, oral automatisms, and can last from three to 20 seconds. Generalised tonic–clonic seizures (GTCS) if present, usually emerge in adolescence, signalling potential syndrome evolution. Myoclonic seizures are not characteristic of CAE.
- ***Epilepsy with myoclonic absence:*** Has an unknown incidence, peaks around seven years and predominantly affects males. Myoclonic absence seizures, characterised by 3-Hz jerks and tonic abduction of arms, are diagnostic features. Associated seizure types include typical absence seizures, GTCS, and myoclonic absence *status epilepticus*.
- ***Epilepsy with eyelid myoclonia (EEM):*** Previously known as Jeavons syndrome, is characterised by frequent eyelid myoclonia induced by eye closure and photic stimulation. Sunflower syndrome, where patients turn their faces to the sun during seizures, is observed in the subgroup with prominent photic induction. While rare, EEM poses challenges in behavioural management, especially in those with intellectual disability.

3. *Developmental and/or epileptic encephalopathies*

EE refer to conditions where epileptic activity exacerbates cognitive and behavioural impairments beyond the expected impact of the underlying cause. They involve frequent epileptiform activity, developmental slowing, and potential regression. Syndromes include:[3]

- ***Epilepsy with myoclonic atonic seizures:*** Previously known as Doose syndrome, it starts in early childhood and may lead to developmental regression during active seizure phases.
- ***Lennox-Gastaut syndrome (LGS)*** is a severe form of DEE with varying aetiologies. LGS is characterised by drug-resistant seizures, cognitive impairments, and specific EEG patterns.
- ***EE and DEE with spike-wave activation in sleep:*** Replace prior designations like epileptic encephalopathy with continuous spike-and-wave in sleep and atypical benign partial epilepsy. Landau–Kleffner syndrome is a subtype, affecting mainly language. Onset is between two and 12 years, with seizures evolving to multiple types. Rare but severe, these syndromes involve EEG abnormalities and cognitive regression, with varied outcomes post-puberty. Structural brain abnormalities, particularly thalamic injuries, correlate with the syndrome.
- ***Febrile infection-related epilepsy syndrome (FIRES):*** A rare condition with an estimated incidence of one per million. FIRES predominantly affects school-aged children. Preceded by a febrile infection, it leads to super refractory *status epilepticus* and has a variable prognosis, with ~10% mortality during the acute phase.
- ***Hemiconvulsion-hemiplegia-epilepsy***

syndrome is an uncommon outcome of focal motor *status epilepticus* in children <4 years, often linked to febrile illnesses. Triggered by focal clonic status epilepticus, it leads to unilateral hemispheric swelling and subsequent atrophy, resulting in drug-resistant focal seizures. Most cases yield a permanent motor deficit, and seizures emerge within three years, often becoming drug-resistant. Surgical intervention may be considered.

Syndromes that may commence at a variable age, encompassing both paediatric and adult patients

This definition includes epilepsy syndromes that begin at variable ages (≤18-years and in those aged ≥19 years). Syndromes can be broadly divided into generalised, focal, and combined generalised and focal epilepsy syndromes. While numerous syndromes emerge in neonates, infants, or children, it's crucial to recognise the onset of epilepsy at various ages to improve patient outcomes. This definition recognises the following groups and subgroups:[4,5]

1. Generalised epilepsy syndromes, with polygenic aetiologies

- ***Juvenile absence epilepsy (JAE):*** Characterised by less-than-daily absence seizures with a distinctive EEG pattern in otherwise normal adolescents. Onset is typically between nine and 13 years, occasionally in adulthood. While often responsive to ASM, lifelong treatment may be necessary. GTCS occur in >90% of cases, usually following absences. Attention deficit hyperactivity disorder, learning difficulties, and mood disorders are common comorbidities. Seizures may last five to 30 seconds, with occasional longer episodes. GTCS vary in frequency. Myoclonic seizures, excluding subtle occurrences during absences, are atypical. JAE, accounting for 2.4%–3.1% of new onset paediatric epilepsy, may be underdiagnosed.
- ***Juvenile myoclonic epilepsy (JME):*** The most common idiopathic generalised epilepsy (IGE) in adolescence and adulthood. It presents with myoclonic and GTCS in neurologically normal individuals. Myoclonic seizures commonly occur post-awakening and are triggered by sleep deprivation. The EEG displays characteristic patterns. While JME is generally drug-responsive, lifelong therapy is often needed. Onset typically ranges from 10 to 24 years, with a slight female preponderance. Seizures may evolve from CAE, and febrile seizures are observed in a small percentage. Cognitive functions are generally normal, but higher rates of anxiety and depression are noted.
- ***Epilepsy with GTCS:*** A common IGE syndrome characterised by GTCS, often induced by sleep deprivation. Onset typically occurs in the second or early third decade, with a low remission rate. Individuals may require lifelong treatment, and seizures, while usually infrequent, can be provoked by factors like sleep deprivation, fatigue, and alcohol. GTCS presents with no other seizure types, distinguishing it from other IGE syndromes like JAE or JME. Rates of anxiety and depression are high in patients living with GTCS.

2. Self-limited focal epilepsy syndromes with presumed complex inheritance.

Subgroups include COVE and POLE. See discussion above.

3. Focal epilepsy syndromes with genetic, structural, or genetic–structural aetiologies.

Subgroups include:

- ***Sleep-related hypermotor/hyperkinetic epilepsy (SHE):*** Replaces previous syndromes like nocturnal frontal lobe epilepsy and is associated with structural abnormalities or specific genes. It has an estimated prevalence of 1.8–1.9 per 100 000 adults and is characterised by clusters of brief motor seizures during sleep with hyperkinetic or asymmetric dystonic/tonic features. SHE is drug-resistant. Onset, often in adolescence, exhibits slight male predominance. Focal motor seizures manifest with vigorous hyperkinetic or tonic/dystonic movements, including autonomic signs and negative emotional expression. While sleep-related onset is common, awake-state seizures occur in 27%–45% of patients.
- ***Familial mesial temporal lobe epilepsy (FMTLE):*** A common syndrome with onset in adolescence or adulthood, involving subtle seizures with *déjà vu* sensations progressing to impaired awareness or tonic–clonic seizures. It constitutes ~20% of non-lesional mesial temporal lobe epilepsy cases, often unnoticed due to its mild presentation. Seizures are associated with normal intellect, no neurological abnormalities, and may include febrile seizures in some cases.
- ***Familial focal epilepsy with variable foci:*** Previously known as familial partial epilepsy with variable foci. Is an autosomal dominant syndrome marked by focal seizures arising from diverse cortical regions, commonly frontal or temporal. Onset is typically in the first or second decade, with a wide age range within families. The syndrome is considered rare. Family member experiences a single seizure type of varying severity. Aetiologies include genetic and structural factors. Most cases respond to ASM, but surgery may be considered for drug-resistant cases with focal cortical dysplasia.
- ***Epilepsy with auditory features (EAF):*** Previously known as autosomal dominant lateral temporal lobe epilepsy. Manifests

in adolescence/adulthood with focal aware seizures featuring auditory symptoms and/or receptive aphasia. Seizures may be triggered by specific sounds, and some individuals experience focal to bilateral tonic–clonic seizures. Inherited in an autosomal dominant fashion, it can present as familial EAF. Onset typically occurs between 10 and 30 years, and outcomes range from spontaneous remission to drug-resistant seizures, with potential surgical intervention for those with structural lesions. Predictors of poor prognosis include early onset, focal epileptiform abnormalities on EEG, and cognitive seizures with complex auditory hallucinations. Seizure types include focal aware sensory and/or cognitive seizures, with additional symptoms like altered vision and reflex seizures precipitated by sound.

- ***Rasmussen syndrome (RS):*** Has an incidence of 1.7–2.4 per 10 million individuals. Onset is typically between one and 10 years, with late-onset cases in adolescence or adulthood. RS is characterised by progressive hemispheric atrophy on neuroimaging, leading to focal seizures, usually motor seizures like *epilepsia partialis continua*. The course involves prodromal, acute, and chronic phases, resulting in frequent drug-resistant seizures and progressive neurological deterioration. Treatment options include hemispherotomy or hemispherectomy. Seizures can manifest as focal aware seizures, evolving into *epilepsia partialis continua* and bilateral tonic–clonic seizures, often progressing to hemiparesis and cognitive impairment.

4. A combined generalised and focal epilepsy syndrome with polygenic aetiology

Epilepsy with reading-induced seizures is a rare epilepsy syndrome marked by reflex myoclonic seizures, particularly orofacial, triggered by reading. If reading persists, seizures can worsen into GTCS. Onset is typically in the late teens, with a male predominance. Seizures affect masticatory muscles, causing clicking sensations or altered speech. Prognosis is generally favourable with ASM. Seizures can be avoided by reducing exposure to the triggering stimulus, but this may limit educational and lifestyle capacities.

5. Epilepsy syndromes with DEE and EE, or both and epilepsy syndromes with progressive neurological deterioration

- ***Progressive myoclonus epilepsies (PME):*** Rare syndromes stemming from diverse genetic causes, marked by myoclonus, progressive motor and cognitive decline, sensory and cerebellar signs, and abnormal EEG patterns in individuals with prior normal development. Photosensitivity is common. PME prevalence varies globally, with a higher incidence in regions favouring consanguineous marriages (marriage between individuals who are closely related). Key PME entities include Unverricht–Lundborg disease (ULD), Lafora disease, neuronal ceroid lipofuscinosis (NCL), and mitochondrial disorders. ULD, prevalent in Scandinavia and Northern Africa, manifests <18 years, often stabilising in early adulthood. Lafora disease, prevalent in Southern Europe and Asia, presents at ages six to 19 years with rapid cognitive decline, ataxia, vision loss, and intractable seizures. NCL, a group of lysosomal storage disorders, involves different forms with distinct genetic causes. Neuronal ceroid lipofuscinosis type 2 (CLN2) (late infantile onset) can exhibit various seizure types, affecting mobility and language, with enzyme replacement therapy available. CLN type 3 (juvenile onset) features visual impairment and milder symptoms. Adult-onset NCL includes types A and B, each with unique clinical presentations and poor prognosis. Genetic testing is crucial for diagnosis, guiding treatment decisions.
- ***FIRES:*** See discussion above.

Conclusions

Precise syndromic diagnosis is paramount for guiding effective epilepsy treatment strategies. The ILAE's classification system has significantly advanced our understanding of epilepsy, categorising syndromes by age groups and associated characteristics.

Early diagnosis is critical, with neonates and infants facing unique challenges, emphasising the importance of recognising distinct syndromes for tailored interventions.

Childhood epilepsy complexities demand specific attention, considering varied manifestations and prognoses. Adult-onset syndromes, like SHE and FMTLE, underscore the necessity for targeted assessments.

Comprehensive awareness of each syndrome aids clinicians in implementing personalised treatments, thereby enhancing patient outcomes and quality of life. SF

References available in the online issue

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Treatment approaches aligned with recent ILAE epilepsy syndromes update

Epilepsy affects >50 million people globally, with an annual cumulative incidence rate of 68 per 100 000 population. Treatment primarily involves anti-seizure medications (ASMs). Accurate clinical classification, as discussed in the first instalment of our two-part series, should guide treatment decisions.[1,2]

About 30% of patients living with epilepsy experience genetic generalised epilepsy (GGE). This category encompasses various syndromes categorised by seizure types and age of onset, including childhood absence epilepsy and juvenile myoclonic epilepsy.[3]

How effective are ASMs?

For those >80 years, the primary and most successful approach to managing epilepsy, has involved the use of ASMs. The goals of ASM therapy are to eliminate or reduce seizures as much as possible, avoid adverse side effects from medication, and to help patients return to normal activities and maintain a normal lifestyle.[4,5]

According to the authors of the third epilepsy genome-wide association study (GWAS), commissioned by the International League against Epilepsy (ILAE) Consortium, the efficacy of current ASM is higher than pharmacotherapies used to treat any other human disease.[1]

Furthermore, their study found that broad-spectrum ASMs (eg valproate, lamotrigine, carbamazepine, topiramate, levetiracetam, lamotrigine, zonisamide, clonazepam, rufinamide) are more effective for GGE compared to narrow-spectrum ASMs, aligning with clinical experience and findings from previous studies.[1,6]

Narrow-spectrum ASMs (eg phenytoin, phenobarbital, carbamazepine, oxcarbazepine, gabapentin, pregabalin, lacosamide, vigabatrin) are used primarily for the treatment of focal seizures.[5,6]

Which ASMs rank the highest?

The *Standard and New Antiepileptic Drugs* (SANAD) studies are the most extensive head-to-head comparisons and randomised controlled trial of ASMs' for focal onset epilepsy (FE) and GGE onset seizures.[2]

Two studies (2007) compared the effectiveness of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate for the treatment of partial epilepsy, and the efficacy of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy, respectively.[7,8]

Arm A of the study showed that lamotrigine was a potential first-line treatment because it was significantly superior to carbamazepine for time to treatment failure, but not significantly different to carbamazepine for time to 12 months of remission. Gabapentin and topiramate were identified as unsuitable first-line treatments. Gabapentin because of poor efficacy and topiramate because of poor efficacy and poor tolerability. Oxcarbazepine was not significantly different from carbamazepine for either outcome.[7]

Arm B of the study showed valproate's superior efficacy for time to treatment failure and 12-month remission compared to the other ASMs included in the study.[8]

The SANAD II study assessed the non-inferiority of levetiracetam compared with valproate for 12-month remission. Levetiracetam did not meet the non-inferiority criteria for time to 12-month remission in the intent-to-treat analysis, and in per-protocol analysis, valproate showed superior remission. Adverse reactions were reported in both groups, but valproate dominated levetiracetam in cost-utility analysis.[3]

More recently, Mishra *et al* used previous GWAS and drugs' activity data and developed a novel method for predicting the relative efficacy of ASM. Their findings confirmed those of arm B of the SANAD studies, indicating that valproate stands out as the most efficacious ASM for GGE onset seizures. In contrast, carbamazepine emerged as the most potent ASM for FE onset seizures, with no other drug demonstrating superior efficacy.[2]

What do guidelines recommend?

The latest National Institute for Health and Care excellence guideline recommend initiation of ASM therapy following a confirmed epilepsy diagnosis or, after a first unprovoked seizure, if certain conditions are met.[9]

Monotherapy is initially recommended, and if unsuccessful, a slow substitution with an alternative is advised. Add-on therapy is considered if monotherapy fails, with continuous monitoring for side effects and seizure reduction.[9]

Individualised treatment plans should be based on classification, age, sex, risk factors, and patient preferences, considering factors like work, school, and family commitments.[9]

Treating epileptic seizures in children, young people and adults

Valproate is recommended as first-line monotherapy for generalised tonic-clonic seizures in boys and men, girls <10 years who are unlikely to require future treatment, and women unable to have children.[9]

Lamotrigine or levetiracetam is suggested for women and girls who plan to start a family. In the event of treatment failure alternative monotherapy or add-on treatment options, such as clobazam, perampanel, or topiramate, can be considered.[9]

For patients with focal seizures, lamotrigine or levetiracetam is recommended as first-line monotherapy, with second-line options like carbamazepine or oxcarbazepine if needed. In case of monotherapy failure, add-on treatment options include carbamazepine,

lacosamide, or topiramate. If add-on treatments are unsuccessful, second-line options like brivaracetam or cenobamate can be considered.[9]

For absence seizures, ethosuximide is suggested as first-line treatment, and valproate can be considered if the first line is ineffective. Lamotrigine or levetiracetam is recommended as second-line options, with alternatives if the first choice proves unsuccessful. Again, special considerations for valproate use in women and girls of childbearing potential are crucial.[9]

Myoclonic seizures in children <4 years require specialist involvement. Valproate can be offered as first-line treatment for boys, men and girls <10-years, and women unable to have children, while levetiracetam is recommended for women and girls who plan to have children.[9]

Tonic or atonic seizures should be managed with valproate as first-line treatment for boys, men, girls <10-years, and women unable to have children. Lamotrigine is considered as a first-line option for women and girls who plan to have children. Further options, including lamotrigine, rufinamide, or topiramate, can be considered if the first-line treatment fails. Ketogenic diets or felbamate may be considered in case of treatment resistance.[9]

For idiopathic generalised epilepsies, valproate is recommended as first-line treatment for boys, men, girls <10 years, and women unable to have children. Lamotrigine or levetiracetam is suggested as first-line options for women and girls who plan to have children, with alternatives if the initial choice is unsuccessful.[9]

Treating childhood-onset epilepsies

Ensuring comprehensive care for individuals with Dravet syndrome, Lennox–Gastaut syndrome, infantile spasms syndrome, self-limited epilepsy with centrotemporal spikes, and epilepsy with myoclonic-atonic seizures involves a systematic approach to treatment.[9]

For patients diagnosed with Dravet syndrome, the primary recommendation is to involve a neurologist with expertise in epilepsy in their care. Valproate is suggested as the first-line treatment due to the severity of the syndrome and limited evidence supporting alternative options.[9]

In cases where valproate is used in women and girls of childbearing age, discussions about potential risks, including those to an unborn child, are crucial.[9]

If valproate monotherapy is ineffective, triple therapy with stiripentol and clobazam is recommended. Second-line options include cannabidiol with clobazam, and if all else fails, potassium bromide may be considered under expert guidance.[9]

For Lennox–Gastaut syndrome, involving a neurologist with epilepsy expertise is essential. Valproate is recommended as the first-line treatment, considering potential risks to women and girls of childbearing age. Lamotrigine is considered as second-line monotherapy or add-on treatment, and if needed, third-line options include cannabidiol with clobazam, clobazam, rufinamide, or topiramate. In cases of ongoing seizures, a ketogenic diet or felbamate may be considered under expert supervision.[9]

Infantile spasms syndrome requires urgent attention from a tertiary paediatric neurologist for rapid assessment and treatment. First-line treatment includes a combination of high-dose oral prednisolone and vigabatrin. Vigabatrin alone is an option, particularly for children at high risk of steroid-related side effects or those with tuberous sclerosis. Second-line options involve a discussion with a paediatric epilepsy specialist, considering ketogenic diet, levetiracetam, nitrazepam, sodium valproate, or topiramate.[9]

Self-limited epilepsy with centrotemporal spikes necessitates a collaborative discussion with children, families, or carers about the potential benefits and risks of treatment. Lamotrigine or levetiracetam is recommended as first-line treatment, with second-line options including carbamazepine, oxcarbazepine, or zonisamide. Sulthiame may be considered as a third-line option under expert guidance.[9]

Epilepsy with myoclonic-atonic seizures involves consultation with a tertiary paediatric neurologist. Levetiracetam or valproate is suggested as first-line treatment, with a ketogenic diet as a second-line option. Third-line choices include clobazam, ethosuximide, topiramate, or zonisamide. Certain medications known to exacerbate seizures, such as carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, and vigabatrin, are discouraged.[9]

Ultimately, discontinuing ASM therapy should be considered for individuals who have been seizure-free for at least two years.[9]

Treating status epilepticus, repeated or cluster seizures, and prolonged seizures

In the event of generalised convulsive *status epilepticus*, immediate resuscitation and emergency treatment are essential for seizures lasting five minutes or more.[9]

Individuals with a personalised emergency management plan should have medication administered according to the plan. For those without such a plan, a first-line treatment involves the prompt use of benzodiazepines, such as buccal midazolam or rectal diazepam. Intravenous (IV) lorazepam is an alternative if resuscitation facilities are available.[9]

Identifying underlying causes, including non-adherence to ASM therapy, is crucial. If the initial treatment is unsuccessful, expert guidance or emergency services should be sought. A second dose of benzodiazepine or IV levetiracetam, phenytoin, or sodium valproate may be considered.[9]

If seizures persist, alternative second-line treatments and third-line options, such as phenobarbital or general anaesthesia, can be considered under expert guidance. Following an episode, an emergency management plan should be agreed upon to address potential recurrence.[9]

For repeated or cluster seizures, the guideline emphasises treating this situation as a medical emergency. Adhering to individualised emergency management plans or promptly administering benzodiazepines, like clobazam or midazolam, is recommended. Seeking expert guidance for further episodes and establishing an emergency management plan with the individual post-seizure are also crucial.[9]

Prolonged convulsive seizures lasting more than the person's usual duration are similarly managed as a medical emergency. Following individualised emergency management plans, if available, or administering benzodiazepines promptly is advised. After such episodes, an emergency management plan should be agreed upon to address concerns of potential recurrence.[9]

Conclusion

ASMs play a pivotal role in managing epilepsy, allowing many patients to lead normal lives. Current evidence, including extensive studies like SANAD, indicates varying efficacy among ASMs, with valproate often standing out. Guided by comprehensive guidelines, individualised treatment plans prioritise patient well-being, reflecting the evolving landscape of epilepsy care. SF

References available in the online issue

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SPECIALIST FORUM

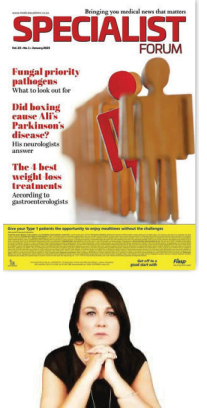
Dear Doc,

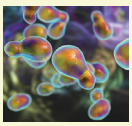
Welcome to the first issue of 2023! Hope you had a wonderful break and are ready to tackle the new year. May the New Year bless you with health, wealth, and happiness!

In this issue, we look at the new American Gastroenterology Association guideline on prescribing weight-loss treatment for patients living with obesity and those who are overweight. To find out which treatment ranked number one, click **here**.

In a recent article, Muhammad Ali's neurologists put an end to speculations that boxing may have caused his Parkinson's disease (PD). It is the first time that Ali's neurologists have spoken on the record about his diagnosis. To find out more about Ali's diagnosis, click **here**.

Regards
René Bosman
Editor: *Specialist Forum*





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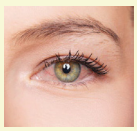

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NEW
S4

VOXIDEX 5 mg/1 mg per ml

Levofloxacin | Dexamethasone

A turning point in post-cataract surgical care[1]

- Potentially halves treatment duration to 7 days.* [2]
- FDC** with simple dosing post cataract surgery to support patient adherence. [1]
- Reduces exposure to antibiotic to align with antimicrobial stewardship practice. [1, 2]
- No dosage adjustment in elderly patients.

In most patients, a 7-day prophylaxis regimen of levofloxacin/dexamethasone successfully controls inflammation and prevents infection, effectively halving the amount of antibiotic used in clinical practice.* [2]

* Many ophthalmologists implement treatment for 2 or more weeks with dose tapering to prevent adverse reactions and clinical relapse. A follow-up, after 1 week, for a decision about whether to stop or continue treatment in patients still experiencing symptoms or inflammation is recommended. [1] Levofloxacin/dexamethasone for 1 week, followed by another week of dexamethasone alone was not inferior to 2 weeks of tobramycin/dexamethasone in preventing or reducing inflammation and in preventing infections. [3]

** FDC - Fixed-dose combination

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