On guard 24/30

Telmisartan offers:
- Sustained 24 hour BP control
- Protection against the early morning BP surge
- Cardiovascular protection

Conveniently packed in 30 tablets.

Tesar 40 mg 30 tablets
Tesar 80 mg 30 tablets

For further product information contact PHARMA DYNAMICS P.O. Box 30958 Tokai Cape Town 7966
Tel 021 707 7000 Fax 021 701 5898 Email info@pharmadynamics.co.za CUSTOMER CARE LINE 0860 PHARMA (742 762) www.pharmadynamics.co.za

SPECIALIST FORUM
A journal for medical professionals

For further product information contact PHARMA DYNAMICS P.O. Box 30958 Tokai Cape Town 7966
Tel 021 707 7000 Fax 021 701 5898 Email info@pharmadynamics.co.za CUSTOMER CARE LINE 0860 PHARMA (742 762) www.pharmadynamics.co.za

Myprodol’s original formulation COMBINES THE DIFFERENT ACTIONS of codeine, ibuprofen and paracetamol in an OPTIMISED RATIO OF 1:20:25 for effective relief of pain, inflammation and fever.\(^1,2\) Myprodol suspension is available in a pleasant blackcurrant flavour.\(^2\)

\(^2\) Myprodol® Suspension approved package insert, June 1994.

Male sexual enhancement pills are considered to be one of the most counterfeited drugs in the world, and South Africans are among the biggest consumers of black market ED drugs.

**Disclaimer:** Please take note that the products featured in this journal are available in South Africa. Products may be marketed under a different name or might not be registered in your country. For more information, contact your local representative.
Here’s to NEW beginnings!

There is change in the life of any magazine. It is with great pleasure that I am able to introduce you to the new look and feel of the The Specialist Forum. This is not merely a cosmetic change, but a substantive makeover in terms of content as well.

We embark on this new journey at a time when the world of journalism is lurching towards an unpredictable digital future and with endless questions being raised about the future of print. In the face of such uncertainty and this gloomy prognosis, we have chosen to swim against the tide and strengthen our commitment to print, which we believe remains relevant and full of potential.

For the design, we have taken a deep content-driven approach. In other words, the design has been used to communicate content rather than compete with it for attention. The effort has been to marry the two seamlessly and produce a look that favours cleanliness over clutter, an easy elegance over exaggerated effect. This new look has been created by our in-house designer, Allison McCallum.

Some things, however, remain the same. The values that have inspired the The Specialist Forum and have earned your trust - such as the commitment to clinical content which is accurate and fair, and to in-depth reporting and analyses - remain unaltered. In an age where journalism sensationalises and uses every trick in the book to grab your attention, never before has the term 'old-fashioned' seemed so comforting and so full of promise.

Change is the new constant, and we accept that. But for us, change also means remaining true to the core values that have made the The Specialist Forum the great magazine that it is.

In this issue, you can expect to find a CPD article by Dr. Claudia Gray on the proper clinical treatment of asthma, an article on the treatment and management of epilepsy and a comprehensive feature on erectile dysfunction (ED).

Further, please allow me to applaud a South African medical professional who recently received one of the world’s most prestigious international accolades. TIME magazine recently named Professor Glenda Gray to the 2017 TIME 100, its annual list of the 100 most influential people in the world. South African-born Gray graduated in 1986 as a medical doctor from the University of Witwatersrand and in 1992 qualified as a paediatrician from the College of Medicine South Africa. Internationally acclaimed for her work in HIV research, Gray has broken new boundaries, redefined scientific excellence and pioneered ground-breaking medical research that has shaped global communities and saved lives.

“Placing people at the centre of health research is the fuel for ensuring impact,” says Professor Gray, currently serving her term as President and CEO of the South African Medical Research Council (SAMRC).

Gray’s story over the years is nothing shy of dedication, commitment, and passion for addressing health issues that have and still affect South Africans.

Most notably, she spearheaded the clinical development of the South African AIDS Vaccine initiative’s HIV vaccines, the SAAVI DNA/MVA candidates and conducted the first trial using these candidate vaccines in South Africa and the United States. In November 2016, an ambitious programme was announced to evaluate an HIV vaccine regimen in South Africa that, if successful, could be the first HIV vaccine to be licensed globally.

Congratulations, Professor Gray! We salute you.

We hope you enjoy this issue of The Specialist Forum as much as we enjoyed creating it for you.

Yours in health

Estene Lotriet
Entrepreneur Russel Pengelly lives a high-energy and driven lifestyle.

In February 2017, the Capetonian found himself between meetings during the sort of fast-paced day typical of running his educational software business. A gym-goer, he’d developed a habit of regularly checking his Apple watch.

“My pulse reading was 160 beats per minute. I put it down to my excitement over developments at work including an overseas trip the following week,” Russel explained. “It was also hot and I’d had about five or six Coke Zeros,” he adds.

“But, in the back of my mind, I knew something was wrong.”

Russel’s concern was justified. His pulse remained elevated all afternoon, through the night and well into his return to Cape Town about 36 hours after his Apple watch had first alerted him to a potential cardiac problem.

After urgent consultation with his GP, an ECG and emergency meds, Russel found himself opposite his cardiologist, who, to Russel’s shock, couldn’t believe he was still alive and ticking. His patient was in a state of extreme Atrial Fibrillation - a quivering or irregular heart beat that can lead to poor blood flow, clots, stroke, heart failure and more. Cardioversion, a technique that uses electricity to treat an abnormal heart rate, returned Russel’s cardiac rhythm to normal levels.

Russel’s vigilance and ability to measure his heart rate in real-time on his Apple watch, proved the ultimate game-changer. “I wanted to use my Apple watch to get healthier through Discovery Vitality, but it ended up saving my life,” reflected Russel.

No limit to high-tech wearables potential for tracking health

Tracking devices are increasingly able to monitor and store a plethora of data points about the person wearing them. For example, the capacity for continual ECG-like measurements aims to see several devices soon predict whether someone is likely to have a heart attack or stroke and give ample warning.

Though not yet on the market, a device similar to the Apple watch and designed to detect atrial fibrillation through a complex algorithm, does in fact exist. The system monitors a user and sends an alert as soon as the threat of stroke or heart attack is detected.

In fact, blood oxygen meter programmes are incubating in the latest versions of the Apple watch and will be activated once medical experts and techies have reached consensus on the details.

Compression shorts, shirts and other such products designed by companies like Athos and Spire are also about to hit global markets. These do everything from tracking blood flow to breathing patterns and correlating readings with levels of anxiety or mindfulness.

“Behaviour modification is most effective when it’s in real time, and we’re just starting to crack that nut,” says top US medical device innovator and founder of Augmedix, Pelu Tran.

Pioneered by non-healthcare companies like Google and Amazon, these data-rich innovations, are also set to uncover patterns and causes of disease as well as predict longevity, in ways yet to be imagined.

If Vitality Active Rewards has been such a powerful driver for making members healthier, what can it do for doctors?

Vitality Active Rewards for Doctors will soon be available, an incentive programme aimed at encouraging our country’s doctors to be healthier. “We’re making it easier for doctors themselves to get active and healthy,” explains Dr Maurice Goodman, Chief Medical Officer at Discovery Health. “Doctors lead busy and stressful lives and often don’t have the time to take proper care of themselves. We care about our country’s doctors and are going to help them to get healthier.”

Modelled on the popular Vitality Active Rewards programme, it will reward doctors for taking care of their own health. “It also incentivises them to do point-of-care screening for chronic conditions for their patients,” adds Goodman.

“Healthcare economics and NCDs worldwide will bankrupt every medical system in the world in next five years. The antidote is leadership,” says Prof Martin Schwellnus. “Every single doctor has to lead by example and inspire younger and older doctors and patients in that way.”

Dr Nossel added that when business puts its weight and resources behind business strategy that addresses social issues, everyone wins. He added, “Helping people to be healthier has always been fundamental to Discovery’s business” Nossel explained that this is what helps to create value for all stakeholders, and a principle that forms the foundation of Discovery’s shared-value insurance model.
Healthcare reimbursement in SA is at a crossroads. Globally, there is a move towards value-based care, while fee-for-service is being phased out. Alternative reimbursement models are being adapted to incorporate outcomes-based reimbursements, which reward the delivery of value by physicians. The quest to curb the rising costs of cancer treatment without sacrificing patient outcomes has successfully been implemented in the US.

The Independent Clinical Oncology Network (ICON) recently hosted an event where Diana Verrilli of McKesson Specialty Health, based in the US, spoke about how value-based care has been successfully implemented in the US Oncology Network.

The principle of value-based care is where funders incentivise doctors for adding value and saving costs, based on measured outcomes. A shift to this kind of reimbursement has been shown to deliver benefits to all stakeholders in the sector - especially the patients.

The ICON team encountered the work of Diana Verrilli on a recent trip to the US as guests of US Oncology, which is the largest oncology network in the US, spanning some 400 sites of care with a membership of around 1400 oncology physicians.

The healthcare situation in the US is not dissimilar to that of SA. Speaking at the event, Dr Jacques Snyman, ISIMO Health CEO, said, “This is an opportunity for us to learn from how the US took ownership of the situation and made value-based care work for them.”

The ICON team encountered the work of Diana Verrilli on a recent trip to the US as guests of US Oncology, which is the largest oncology network in the US, spanning some 400 sites of care with a membership of around 1400 oncology physicians.

The principle of value-based care is where funders incentivise doctors for adding value and saving costs, based on measured outcomes. A shift to this kind of reimbursement has been shown to deliver benefits to all stakeholders in the sector - especially the patients.

The ICON team encountered the work of Diana Verrilli on a recent trip to the US as guests of US Oncology, which is the largest oncology network in the US, spanning some 400 sites of care with a membership of around 1400 oncology physicians.

The principle of value-based care is where funders incentivise doctors for adding value and saving costs, based on measured outcomes. A shift to this kind of reimbursement has been shown to deliver benefits to all stakeholders in the sector - especially the patients.

The ICON team encountered the work of Diana Verrilli on a recent trip to the US as guests of US Oncology, which is the largest oncology network in the US, spanning some 400 sites of care with a membership of around 1400 oncology physicians.

Why should oncologists make this change? One can look at this from the perspective of ‘change before you have to’ and ‘take control before someone else does’. Payer mergers and unsustainable drug costs are drivers of this trend. The idea is not to compromise care. Quite the opposite, in fact. The programme’s goal is to improve care but lower the cost. The premise being that improving access to care and adding enhanced services will result in better care as well as smarter spending, and healthier patients.

“What we never do in these models is reduce fees to participate and hope for an upside. The rates will stay the same. Talk about the work flow to keep it sustainable. This takes time,” she concluded.
COPD is the fourth leading cause of death in the world. The main culprits are inhaled cigarette smoke and exposure to other noxious particles such as smoke from biomass fuels that cause lung inflammation.

According to the authors of the guideline, this chronic inflammatory response may induce parenchymal tissue destruction, resulting in emphysema. This disrupts the normal repair and defense mechanisms, causing small airway fibrosis. These pathological changes lead to air trapping and progressive air flow limitation, and in turn to breathlessness and other characteristic symptoms of COPD.

Symptoms

Chronic and progressive dyspnoea, cough, sputum production that can be variable from day-to-day, dyspnoea (increased effort to breathe, heaviness, air hunger, or gasping), chronic cough as well as wheezing and chest tightness (according to the authors) an absence of wheezing or chest tightness does not exclude a diagnosis of COPD, nor does the presence of these symptoms confirm a diagnosis of asthma). Fatigue, weight loss and anorexia are common problems in patients with severe and very severe COPD.

Pharmacological options

Pharmacologic therapy for COPD is used to reduce symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance. The choice within each class depends on the availability and cost of medication and the patient’s response.

The classes of medications commonly used in treating COPD are:

Influenza and pneumococcal vaccination should be offered to every COPD patient. They appear to be more effective in older patients and those with more severe disease or cardiac comorbidity.

Non-surgical bronchoscopic lung volume reduction techniques should not be used outside clinical trials.

In patients who smoke, smoking cessation is very important. Pharmacotherapy and nicotine replacement reliably increase long-term smoking abstinence rates. Appropriate pharmacologic therapy can reduce COPD symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance.

To date, none of the existing medications for COPD has been shown conclusively to modify the long-term decline in lung function. Each pharmacological treatment regimen needs to be patient-specific, guided by severity of symptoms, risk of exacerbations, drug availability, and the patient’s response.

All patients who get short of breath when walking on their own pace on level ground should be offered rehabilitation. It can improve symptoms, quality of life, and physical and emotional participation in everyday activities.

In patients who smoke, smoking cessation is very important. Pharmacotherapy and nicotine replacement reliably increase long-term smoking abstinence rates. Appropriate pharmacologic therapy can reduce COPD symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) recently updated their treatment guideline for chronic obstructive pulmonary disease (COPD). In this article, we will focus on a brief overview of COPD, treatment options and drug recommendations.
Bronchodilators
Increase the FEV1 or change other spirometric variables, usually by altering airway smooth muscle tone, are termed bronchodilators. Bronchodilators improve emptying of the lungs, tend to reduce dynamic hyperinflation at rest and during exercise, and improve exercise performance. The extent of these changes, especially in severe and very severe patients, is not easily predictable from the improvement in FEV1. Bronchodilator medications are given on either an as-needed basis or a regular basis to prevent or reduce symptoms.

Beta2-agonists
The principal action of beta2-agonists is to relax airway smooth muscle by stimulating beta2-adrenergic receptors, which increases cyclic adenosine monophosphate (cAMP) and produces functional antagonism to bronchoconstriction. The bronchodilator effects of short-acting beta2-agonists usually wear off within four to six hours. Regular and as-needed use of short-acting beta2-agonists improve FEV1 and symptoms.

The use of high doses of short-acting beta2-agonists on an as-needed basis in patients already treated with long-acting bronchodilators is not supported by evidence, may be limited by side effects, and cannot be recommended. For single-dose, as-needed use in COPD, there appears to be no advantage in using levalbuterol over conventional bronchodilators.

Long-acting inhaled beta2-agonists show duration of action of 12 or more hours. Formoterol and salmeterol significantly improve FEV1 and lung volumes, dyspnoea, health-related quality of life and exacerbation rate, but have no effect on mortality and rate of decline of lung function.

A systematic review of trials of salmeterol and formoterol showed a significant reduction in the numbers of patients requiring treatment for exacerbations and the number requiring hospitalisation. Salmeterol reduces the rate of hospitalisation. Indacaterol is a once daily beta2-agonist with a duration of action of 24 hours. The bronchodilator effect is significantly greater than that of formoterol and salmeterol, and similar to tiotropium. Indacaterol has significant effects on breathlessness, health status and exacerbation rate. Its safety profile is similar to placebo. In clinical trials a significant number of patients (24% versus 7%) experienced cough following the inhalation of indacaterol.

Anticholinergics
The most important effect in COPD patients of anticholinergic medications, such as ipratropium, oxitropium and tiotropium bromide, appears to be blockage of acetylcholine’s effect on muscarinic receptors.

Current short-acting drugs block M2 and M3 receptors and modify transmission at the pre-ganglionic junction, although these effects appear less important in COPD. The long-acting anticholinergic tiotropium has a pharmacokinetic selectivity for the M3 and M1 receptors.

The bronchodilating effect of short-acting inhaled anticholinergics lasts longer than that of short-acting beta2-agonists, with some bronchodilator effect generally apparent up to eight hours after administration.

Among long-acting anticholinergics, aclidinium has a duration of at least 12 hours whereas tiotropium and glycopyrronium have a duration of action of more than 24 hours. Tiotropium reduces exacerbations and related hospitalisations, improves symptoms and health status, and improves the effectiveness of pulmonary rehabilitation. In a large, long-term clinical trial on patients with COPD, there was no effect of tiotropium added to other standard therapies on the rate of lung function decline and no evidence of CV risk.

The long-acting anticholinergics aclidinium and glycopyrronium seem to have similar action on lung function and breathlessness as tiotropium, whereas far less data are available for other outcomes.

Methylxanthines
Controversy remains about the exact effects of xanthine derivatives. They may act as nonselective phosphodiesterase inhibitors, but have also been reported to have a range of non-bronchodilator actions, the significance of which is disputed. Data on duration of action for conventional, or even slow-release, xanthine preparations are lacking in COPD.

Theophylline, the most commonly used methylxanthine, is metabolised by cytochrome P450 mixed function oxidases. Theophylline is less effective and less well tolerated than inhaled long-acting bronchodilators and is not recommended if those drugs are available and affordable. However, there is evidence for a modest bronchodilator effect compared with placebo in stable COPD. There is also some evidence of symptomatic benefit compared to placebo.

Addition of theophylline to salmeterol produced a greater improvement in FEV1 and breathlessness than salmeterol alone. Low-dose theophylline reduces exacerbations but does not improve post-bronchodilator lung function.

Methylxanthines have a wide range of toxic effects. Problems include the development of atrial and ventricular arrhythmias (which can prove fatal) and grand mal convulsions (which can occur irrespective of prior epileptic history). Other side effects include headaches, insomnia, nausea, and heartburn, and these may
SOLPHYLLEX® IS THE EFFECTIVE 3-IN-1 SOLUTION THAT HELPS RELIEVE A COUGH associated with respiratory infection

Solphylllex® Syrup

Cough Syrup, Expectorant and Bronchodilator

200 ml

Fast acting cough syrup to alleviate tight chest

adcock ingram
occur within the therapeutic range of serum theophylline.

These medications also have significant interactions with commonly used medications such as digitalis, coumadin, etc. Unlike the other bronchodilator classes, xanthine derivatives may involve a risk of overdose (either intentional or accidental).

**Combination bronchodilator therapy**

Combining bronchodilators with different mechanisms and durations of action may increase the degree of bronchodilation for equivalent or lesser side effects. For example, a combination of a short-acting beta₂-agonist and an anticholinergic produces greater and more sustained improvements in FEV₁ than either drug alone and does not produce evidence of tachyphylaxis over 90 days of treatment.

The combination of a beta₂-agonist, an anticholinergic, and/or theophylline may produce additional improvements in lung function and health status. Short-term combination therapy using formoterol and tiotropium has been shown to have a bigger impact on FEV₁ than the single components.

Combinations of short-acting beta₂-agonists and anticholinergics are also superior compared to either medication alone in improving FEV₁ and symptoms. Combinations of a long-acting beta₂-agonist and a long-acting anticholinergic have shown a significant increase in lung function whereas the impact on patient reported outcomes is still limited.

There is still too little evidence to determine if a combination of long-acting bronchodilators is more effective than a long-acting anticholinergic alone for preventing exacerbations.

**Corticosteroids**

**Inhaled corticosteroids**

The dose-response relationships and long-term safety of inhaled corticosteroids in COPD are not known. Only moderate to high doses have been used in long-term clinical trials. The efficacy and side effects of inhaled corticosteroids in asthma are dependent on the dose and type of corticosteroid, but whether this is also the case in COPD is unclear. The effects of corticosteroids on pulmonary and systemic inflammation in patients with COPD are controversial, and their role in the management of stable COPD is limited to specific indications.

Regular treatment with inhaled corticosteroids improves symptoms, lung function, and quality of life, and reduces the frequency of exacerbations in COPD patients with an FEV₁ <60% predicted.

Withdrawal from treatment with inhaled corticosteroids may lead to exacerbations in some patients, although in another study with severe and very severe COPD patients, inhaled corticosteroids could be gradually withdrawn over a three- month period without increasing the medium term risk of exacerbations, although lung function deteriorated significantly. Withdrawal of inhaled corticosteroids, in COPD patients at low risk of exacerbation, can be safe provided that patients are left on maintenance treatment with long-acting bronchodilators.

Regular treatment with inhaled corticosteroids does not modify the long-term decline of FEV₁ nor mortality in patients with COPD.

**Combination inhaled corticosteroid/bronchodilator therapy**

An inhaled corticosteroid combined with a long-acting beta₂-agonist is more effective than the individual components in improving lung function and health status and reducing exacerbations in patients with moderate to very severe COPD.

An inhaled corticosteroid/long-acting beta₂-agonist combination given once daily does not show relevant differences regarding efficacy compared to twice daily. A large prospective clinical trial failed to demonstrate a statistically significant effect of combination therapy on mortality, but a subsequent meta-analysis found that combination therapy may reduce mortality with a number needed to treat (NNT) of 36 254.

Combination therapy is associated with an increased risk of pneumonia, but no other significant side effect. The addition of a long-acting beta₂-agonist/inhaled corticosteroid combination to tiotropium improves lung function and quality of life and may further reduce exacerbations, but more studies of triple therapy are needed.

**Oral corticosteroids**

Oral corticosteroids have numerous side effects. An important side effect of long-term treatment of COPD with systemic corticosteroids is steroid myopathy, which contributes to muscle weakness, decreased functionality, and respiratory failure in subjects with very severe COPD.

In view of the well-known toxicity of long-term treatment with oral corticosteroids, prospective studies on the long-term effects of these drugs in COPD are limited. However, systemic corticosteroids for treating acute exacerbations have been shown to improve symptoms, lung function, reduce rate of treatment failure, and shorten length of hospital stay.

The effect of preventing a subsequent exacerbation has been shown in a pooled data analysis and it was demonstrated that systemic corticosteroids when being used to treat acute exacerbations can reduce 30-day readmission rates due to recurrent exacerbations.

**Phosphodiesterase-4 inhibitors**

The principal action of...
Phosphodiesterase-4 inhibitors is to reduce inflammation by inhibiting the breakdown of intracellular cyclic AMP. It is a once daily oral medication with no direct bronchodilator activity, although it has been shown to improve FEV1 in patients treated with salmeterol or tiotropium. Roflumilast reduces moderate and severe exacerbations treated with corticosteroids by 15%-20% in patients with chronic bronchitis, severe to very severe COPD, and a history of exacerbations.

The effects on lung function are also seen when roflumilast is added to long-acting bronchodilators. There are no direct comparison or add-on studies of roflumilast and inhaled corticosteroids. Phosphodiesterase-4 inhibitors should always be used in combination with at least one long-acting bronchodilator.

Phosphodiesterase-4 inhibitors have more adverse effects than inhaled medications for COPD. The most frequent adverse effects are nausea, reduced appetite, abdominal pain, diarrhoea, sleep disturbances, and headache.

Adverse effects led to increased withdrawal in clinical trials from the group receiving roflumilast. Adverse effects seem to occur early during treatment, are reversible, and diminish over time with continued treatment.

In controlled studies an average unexplained weight loss of two kilogramme has been seen and weight monitoring during treatment is advised as well as avoiding treatment with roflumilast in underweight patients. Roflumilast should also be used with caution in patients with depression. Roflumilast and theophylline should not be given together.

**Oxygen therapy**
The long-term administration of oxygen (>15 hours per day) to patients with chronic respiratory failure has been shown to increase survival in patients with severe resting hypoxemia. Long-term oxygen therapy is indicated for patients who have PaO₂ at or below 7.3 kPa (55mmHg) or SaO₂ at or below 88%, with or without hypercapnia confirmed twice over a three-week period.

**Ventilatory support**
Non-invasive ventilation (NIV) is increasingly used in patients with stable very severe COPD. Randomised controlled trials provide contradictory results regarding the clinical benefits of long-term NIV in patients with COPD and chronic hypercapnia, especially in terms of health status.

**Surgical treatments**
Lung volume reduction surgery (LVRS) is a surgical procedure in which parts of the lung are resected to reduce hyperinflation, making respiratory muscles more effective pressure generators by improving their mechanical efficiency (as measured by length/tension relationship, curvature of the diaphragm, and area of apposition).

In addition, an LVRS increase the elastic recoil pressure of the lung and thus improves expiratory flow rates and reduces exacerbations. The advantage of surgery over medical therapy is more significant among patients with predominantly upper-lobe emphysema and low exercise capacity prior to treatment. A prospective economic analysis indicated that LVRS is costly relative to healthcare programmes not including surgery. In contrast to medical treatment, LVRS has been demonstrated to result in improved survival (54% versus 39.7%) in severe emphysema patients with upper-lobe emphysema and low post-rehabilitation exercise capacity. In similar patients with high post-pulmonary rehabilitation exercise capacity no difference in survival was noted after LVRS, although health-related quality of life and exercise capacity improved.

LVRS has been demonstrated to result in higher mortality than medical management in severe emphysema patients with an FEV1 ≤20% predicted and either homogeneous emphysema on high resolution computed tomography or a diffusing capacity for carbon monoxide (DLco) ≤20% predicted.

**Lung transplantation**
In appropriately selected patients with very severe COPD, lung transplantation has been shown to improve quality of life and functional capacity. The common complications seen in COPD patients after lung transplantation, apart from post-operative mortality, are acute rejection, bronchiolitis obliterans, opportunistic infections such as cytomegalovirus, fungal (candida, aspergillus, cryptococcus, pneumocystis) or bacterial (pseudomonas, staphylococcus species) infections, and lymphoproliferative disease.

Lung transplantation is limited by the shortage of donor organs and costs. Criteria for referral for lung transplantation include COPD with a Body-mass index, airflow Obstruction, Dyspnea, and Exercise (BODE) index exceeding five.

Recommended criteria for listing include a BODE index of seven to ten and at least one of the following: History of exacerbation associated with acute hypercapnia (PaCO₂ >6.7kPa [50mmHg]), pulmonary hypertension, cor pulmonale, or both despite oxygen therapy and FEV1 <20% predicted with either DLco <20% predicted or homogenous distribution of emphysema.

**Source:** Global Strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. Updated 2016.
The goal of asthma treatment is to achieve control of the disease for prolonged periods, taking into account the safety and cost of treatment required to achieve this. This article provides a brief overview of treatments available for asthma maintenance treatment, as well as newer therapeutic options.

1. Implementing treatment for chronic asthma

**Avoidance of triggers**, wherever possible, helps to minimise asthma severity and reduces asthma exacerbations. This includes avoidance of exposure to personal and second-hand tobacco smoke, reduction in exposure to furry animals, pollen, house dust mite and other allergens in those asthmatics known to be allergic, avoidance of sensitisers and irritants (dust and fumes) which aggravate or cause asthma, and avoidance of drugs that may aggravate asthma such as β blockers, aspirin and nonsteroidal anti-inflammatory drugs.

**Pharmacotherapy** is the cornerstone of asthma management, with appropriate medications and delivery devices to meet patients’ needs and circumstances.

When asthma is first diagnosed, it is convenient for implementation of treatment to classify it by **SEVERITY** as mild intermittent or chronic persistent asthma that is mild, moderate or severe.

After therapy is initiated, the emphasis for clinical management changes to the **assessment of asthma CONTROL**, which is the degree to which the manifestations of asthma are minimised by therapeutic intervention and the goals of therapy are met.
2. Routes of administration of asthma drugs

Asthma treatment can be administered in different ways - inhaled, orally or parenterally (by subcutaneous, intramuscular, or intravenous injection). The major advantage of inhaled therapy is that drugs are delivered directly into the airways, producing higher local concentrations with significantly less risk of systemic side effects. Inhaled medications for asthma are available as pressurised metered-dose inhalers (pMDIs), breath-actuated MDIs, dry powder inhalers (DPIs), soft mist inhalers, and nebulisers (rarely indicated for the treatment of chronic asthma). Choice of delivery device should be based on correct technique and patient preference, and be assessed during asthma reviews. Most patients make mistakes with a pMDI alone. They are less likely to do so if they also use a large volume (500 ml) spacer or holding chamber to improve drug delivery, increase lung deposition, and reduce local and systemic side effects.

3. Classification of asthma drugs

A classification of asthma drugs based on current knowledge of their mode of action is represented in Table 3. They may be:

- **Relievers** - short-acting bronchodilators with rapid onset of action that provide acute relief of symptoms
- **Controllers** - drugs with anti-inflammatory activity and/or a sustained bronchodilator action. Treatment combinations are necessary in patients with more severe asthma or mild asthma not responsive to low dose inhaled corticosteroids.

### 3.1 Controllers

There are two groups of controllers - those with anti-inflammatory action (corticosteroids and leukotriene blockers) and those with a sustained bronchodilator action (long-acting β2 agonists, long acting anti-cholinergics and slow-release theophyllines).

Anti-inflammatory treatment is recommended for all patients with chronic persistent asthma. Inhaled corticosteroids are the most widely studied and recommended drugs in this class. Leukotriene modifiers are effective, but less so than inhaled corticosteroids. Theophyllines have also been shown to have weak anti-inflammatory effects.

#### 3.1.1 Corticosteroids

**3.1.1.1 Inhaled corticosteroids (ICS)**

Inhaled corticosteroids are the mainstay of treatment for patients with chronic persistent asthma. The inhaled route is preferred because delivery directly to the lungs permits the use of lower doses.

Through their anti-inflammatory effects, inhaled corticosteroids reduce airway inflammation, decrease bronchial hyperresponsiveness and improve asthma control. In addition, they may modify airway remodelling and prevent an accelerated decline in lung function. Their long-term use in adequate doses has been shown to decrease exacerbations and mortality. There are several inhaled corticosteroids available and their equivalent doses in comparison with beclomethasone dipropionate (BDP) are shown in Table 1.

Systemic absorption of inhaled corticosteroids arises from oropharyngeal absorption and to a lesser extent from drug deposited in the lungs. This may be reduced by the use of a spacer device combined with mouth washing after inhalation. The former increases the fraction delivered to the lung. Both measures reduce the incidence of local side effects such as dysphonia and oropharyngeal candidiasis.

Inhaled corticosteroids are generally administered twice daily, but budesonide and cilengitide are also approved for once daily use in milder asthma. A low starting dose is 200-500 μg/day of BDP equivalent and a dose above 1000 μg/day is considered a high dose. At higher doses, the dose-response curve is relatively flat but the risk of systemic side effects may be increased.

In older children and adults, a preferred strategy to reduce the dose of corticosteroids and improve control is the combination of long-acting β2 agonists (salmeterol or formoterol) with lower doses of inhaled corticosteroids. An alternative is the combination of lower dose inhaled corticosteroids with leukotriene blockers, which is a preferred combination in younger children. If these are unavailable, combination with slow-release theophyllines is a weaker alternative. Long-acting β2 agonists and slow-release theophylline must always be used in combination with at least low dose corticosteroids.

### Table 1: Low, medium and high doses of inhaled corticosteroids: estimated clinical comparability

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adults and adolescents ≥12 years</th>
<th>Children 6-11 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Daily dose (mcg)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>Medium</td>
</tr>
<tr>
<td>Beclomethasone dipropionate CFC</td>
<td>200-500</td>
<td>&gt;500-1000</td>
</tr>
<tr>
<td>Beclomethasone dipropionate HFA</td>
<td>100-200</td>
<td>&gt;200-400</td>
</tr>
<tr>
<td>Budesonide (DPI or HFA)</td>
<td>200-400</td>
<td>&gt;400-800</td>
</tr>
<tr>
<td>Ciclesonide HFA</td>
<td>80-160</td>
<td>&gt;160-320</td>
</tr>
<tr>
<td>Mometasone furoate (DPI)</td>
<td>80</td>
<td>n/a</td>
</tr>
<tr>
<td>Fluticasone furoate (DPI)</td>
<td>200-250</td>
<td>&gt;250-500</td>
</tr>
<tr>
<td>Fluticasone propionate (DPI)</td>
<td>100-250</td>
<td>&gt;250-500</td>
</tr>
<tr>
<td>Fluticasone propionate (HFA)</td>
<td>100-250</td>
<td>&gt;250-500</td>
</tr>
<tr>
<td>Mometasone furoate</td>
<td>110-220</td>
<td>220-440</td>
</tr>
</tbody>
</table>

Asthma treatment can be administered in different ways - inhaled, orally or parenterally.
for maintenance treatment of asthma.

The inhaled corticosteroid dose should be adjusted according to the level of control attained. Once control of asthma is achieved, the dose of medication should be carefully titrated to the minimum dose required to maintain control, thus reducing the potential for adverse effects.

Nebulised corticosteroids are expensive, require high-pressure nebulisers for optimal delivery, and are not recommended for routine use in chronic asthma.

Side effects
Most studies evaluating the systemic effects of ICS suggest that clinically effective doses of ICS are safe and the potential risks are well balanced by the clinical benefits. However, studies using higher doses have been associated with detectable systemic effects on both growth and the hypothalamo-pituitary (HPA) axis. Although there are fewer studies in children younger than five years, the available data are similar to those from older children. Generally, low doses of ICS have not been associated with any clinically important adverse systemic effects in clinical trials, and long-term use is considered safe. Local side effects, such as hoarseness and candidiasis, can occur, but are rare when a spacer is used.

Efficacy in children
Most children are controlled on low daily doses of ICS (100–200 μg budesonide or equivalent). Some children require higher doses (400 μg/day) for control and for protection against exercise-induced symptoms. Clinical improvement occurs rapidly within 1-2 weeks, although maximum improvement may occur only after many weeks. Symptoms may recur after stopping ICS, with control deteriorating within weeks.

Several studies of ICS in young children under the age of five years with asthma have shown similar clinical effects to those in older children, including increases in lung function and number of symptom-free days, and a reduction in symptoms, need for additional medication, caregiver burden, systemic glucocorticosteroid use, and exacerbations. In young children, use of ICSs for up to two years has not been shown to induce remission of asthma; symptoms usually return when treatment is stopped.

3.1.1.2 Oral corticosteroids
Oral corticosteroids are widely used for acute exacerbations of asthma at doses of 1-2 mg/kg/day for 3-7 days. Longer-term oral corticosteroids may be considered in patients with poorly controlled asthma on high doses of inhaled corticosteroids and additional controller medications. Long-term oral corticosteroids (> 7.5 mg prednisone/day), while relatively inexpensive, are associated with serious systemic side effects, including growth suppression, obesity and adrenal suppression. Patients for whom long-term corticosteroids are being considered should be referred to a specialist for review. Alternate day dosing may reduce side effects. In patients on oral steroids, increased dosage should be given during episodes of increased stress, e.g. surgery.

3.1.2 Leukotriene modifiers
Leukotriene modifiers (e.g. montelukast) are orally administered and act to antagonise the leukotriene receptor and thus resulting in an anti-inflammatory action via a different pathway to corticosteroids. They have a rapid onset of action (1-3 hours) and have been shown to exert their effect within days of commencing treatment. They may be used in patients with at least mild persistent asthma as add-on treatment to inhaled corticosteroids and may be of value in patients with aspirin-sensitive asthma and exercise induced asthma in combination with inhaled corticosteroids. As
add-on treatment in children whose asthma is insufficiently controlled by low doses of inhaled glucocorticosteroids, leukotriene modifiers provide moderate clinical improvements, including a significant reduction in exacerbations. Not all patients respond, so if no benefit is evident after four weeks, the leukotriene modifiers should be withdrawn.

Leukotriene receptor antagonists are safe and effective for treatment of asthma in young children, from as early as six months of age. In pre-school children,LTRAs have been proposed as alternative first-line therapy to ICSs for episodic or mild persistent asthma, particularly in children who have difficulty in utilising inhalation treatment, with poor compliance, or with exercise-induced bronchospsasm (EIB). Their routine use as monotherapy in asthma in adults is not advised. Another potential role for leukotriene modifiers is in those patients with co-morbid asthma and allergic rhinitis, as their anti-inflammatory action extends from the nasal mucosa to the bronchial tree. This is in line with the concept of the ‘united air way’ disease in which asthma and allergic rhinitis are regarded as manifestations of a single disorder, and treating one disease may affect the control of the other.

Side effects
Leukotriene modifiers are generally very well tolerated. Headaches and gastrointestinal upset are the most commonly encountered side effects. Skin rashes or flu like symptoms are much less common. Post marketing surveillance has shown agitation, irritability, anxiety, insomnia and nightmares in a small proportion of patients.

3.1.3 Long-acting β2 agonists (LABAs)
Salmeterol and formoterol are LABAs currently available in SA and are administered twice daily. LABAs can be added to low to medium doses of inhaled corticosteroids instead of increasing the dose of inhaled corticosteroid further. They are useful for control of nocturnal symptoms and exercise-induced asthma. Studies have reported improvements in peak flow and lung function with the addition of a LABA. However, the effect on symptoms, need for rescue medication and frequency of exacerbations has been less consistent. LABAs as monotherapy have been associated with an increase in asthma-related mortality so they must always be taken together with an inhaled corticosteroid. Combination products (i.e. those containing an inhaled corticosteroid and a LABA in the same device) are preferable to administration via separate inhalers. Fixed combination inhalers ensure that the LABA is always accompanied by an ICS. Combination products available in South Africa are fluticasone/salmeterol and budesonide/formoterol. Newer inhaled steroid/LABA combinations include fluticasone furoate/vilanterol and mometasone furoate/formoterol will soon be available in SA.

LABAs have been inadequately studied in children under four years of age, so are currently not recommended in this age group. Some patients may not respond to LABAs. LABAs are generally well tolerated. Side effects are similar in type and frequency to those of short-acting bronchodilators (SABAs), and include muscle tremor, headache and palpitations. Both salmeterol and formoterol have sustained bronchodilator activity, but differ in the time of onset of action. The time of onset of salmeterol is delayed but formoterol has a rapid onset of bronchodilation (within 10-15 minutes of administration) similar to that of short-acting B2 agonists. In addition, formoterol has a wider dose range, whereas salmeterol has an upper dose limit of 50ug bd. Formoterol / ICS combinations are thus suitable to be used for both control and relief of asthma symptoms.

3.1.4 Slow-release (SR) Theophyllines
Theophylline can be used in the treatment of asthma mainly as a bronchodilator (10-20 mg/kg/day), though it may also have anti-inflammatory effects at lower doses (5-10 mg/kg/day). The anti-inflammatory effects of theophylline are small (less than that of low-dose ICSs) and side effects are common.

Theophylline may be used as alternative, adjunctive therapy with ICSs in children older than five years old and in adults. They should not be used as monotherapy. Most formulations of SR theophyllines have a 12 hour and some a 24 hour duration of action. They are administered orally. There is no role for oral short-acting theophyllines in chronic asthma. Their disadvantages include a narrow therapeutic range, drug interactions and frequent side effects (nausea, vomiting, abdominal pain, gastro-oesophageal reflux, palpitations, insomnia, irritability and seizures). More serious side effects such as arrhythmias and gastric bleeding may occur. These side effects are mainly seen at doses > 10 mg/kg/day. The risk of adverse effects is reduced if treatment is initiated with daily doses around 5 mg/kg/day and then gradually increased to 10 mg/kg/day. Severe overdosing with theophylline can be fatal.

Monitoring of serum theophylline concentration is essential. Long-term treatment with theophylline is not generally recommended in young children because of its adverse effects.
3.1.5 Other long term treatment options

Immunotherapy

Allergen immunotherapy should be considered for patients who have persistent asthma if there is clear evidence of a relationship between symptoms and exposure to an allergen to which the patient is sensitive.

Both subcutaneous and sublingual immunotherapy has an effect on inflammatory parameters and bronchial hyperreactivity in asthmatics sensitised to house dust mites. Sublingual immunotherapy is the safer option and could be used as adjunctive treatment to pharmacotherapy in adults and children older than five years old with rhinitis and mild to moderate asthma (FEV1 >80%), to enhance asthma control.

Anticholinergics

including methotractate may rarely be of benefit in refractory asthmatics. Patients considered for this treatment must be referred to a specialist.

Antihistamines are ineffective in the treatment and prevention of asthma.

Dietary changes

There is little scientific evidence that exclusion diets are useful in the treatment of asthma. As such, they are not routinely recommended.

Several cross-sectional studies have shown that low serum levels of Vitamin D are linked to impaired lung function, higher exacerbation frequency and reduced corticosteroid response. However, to date, Vitamin D supplementation has not been associated with improvement in asthma control or reduction in exacerbations.

4. “Newer” treatment modalities for asthma

4.1 Long Acting Anti-Cholinergics

Tiotropium bromide is an inhaled, once daily anticholinergic bronchodilator which binds to all three muscarinic receptors to produce a long acting bronchodilator effect and possibly an anti-inflammatory effect. It was initially approved for COPD, but recently (2015) added on as a late step in adult chronic asthma guidelines as a treatment option in patients with uncontrolled asthma despite high doses of inhaled corticosteroids and LABAs. Tiotropium is available as a dry powder inhaler or pMDI, and is licensed for adults and adolescents over the age of 12 years in a once daily dose. Studies have shown an improvement in lung functions and a reduction in exacerbations in patients with uncontrolled asthma.

4.2 Monoclonal antibodies

4.2.1 Omalizumab (anti IgE)

Omalizumab is a recombinant humanised monoclonal anti-IgE antibody. It binds free IgE in blood and interstitial fluid and to the membrane-bound form of IgE on the surface of mIgE-expressing B-lymphocytes.

It is licensed as an add-on treatment in severe persistent asthma in adults, adolescents and children over the age of six years with evidence of allergic sensitisation and IgE levels of up to 1500 kU/L. There is also some evidence for its efficacy at higher IgE levels. Studies have shown improvement in quality of life as well as reductions in severe exacerbations in patients on omalizumab. Omalizumab is given subcutaneously every 2-4 weeks and courses of at least six months are recommended for severe asthma in suitable patients.

4.2.2 Mepolizumab (anti interleukin-5)

Mepolizumab is a fully humanised anti-interleukin 5 (IL-5) monoclonal IgG1 antibody that binds to free IL5 and prevents its association with the IL5 receptor on eosinophils. In clinical trials it has been shown to reduce airways and blood eosinophils and reduce asthma exacerbations. Mepolizumab has recently been added on to the step-up guidelines for severe asthma uncontrolled on high dose inhaled steroids and LABAs. It should be given in specialist referral centres only and is licensed for over the age of 12 years.

4.2.3 Dupilumab (anti interleukin 4)

Dupilumab is a fully human monoclonal antibody directed against the body’s interleukin (IL)-4 receptors, intended to inhibit the downstream effects of type 2 mucosal immunity cytokines, IL-4 and IL-13. Both are cytokines believed to play a major role in the manifestation of allergic diseases. Studies have shown dupilumab to be efficacious as an add-on therapy to medium-to-high-dose inhaled corticosteroids plus a long-acting β2 agonist in patients with uncontrolled persistent asthma. Improvement has been demonstrated in baseline forced expiratory volume in 1 s (FEV1), as well as a reduction in annualised exacerbation rates and improvements in quality of life and asthma control. Efficacy was more evident when injections were given every two weeks compared with every four weeks.

Treatment algorithms for the management of chronic asthma in accordance with GINA (Global Initiative for Asthma) guidelines 2016 are advised.

5. Stepping down asthma treatment

Consider stepping down when asthma symptoms have been well controlled and lung function has been stable on medium-to-high-dose inhaled corticosteroids and LABAs. Consider stepping down when asthma symptoms have been well controlled and lung function has been stable for three or more months. This should be done under close supervision. Asthma is considered well controlled if:

- ≤ 2 daytime symptoms/week
- No limitation of activities
- No nocturnal symptoms/awakenings
### Multiple choice questions

<table>
<thead>
<tr>
<th>SURNAME</th>
<th>INITIALS</th>
</tr>
</thead>
<tbody>
<tr>
<td>YOUR HPCSA REGISTRATION NO.</td>
<td>MP</td>
</tr>
</tbody>
</table>

**Address:**

**Telephone:**

**Fax:**

**E-mail:**

**YES!** I would like to receive *The Specialist Forum* for FREE monthly.

**INSTRUCTIONS:**

To complete the questionnaire online, go to [www.specialistforum.co.za](http://www.specialistforum.co.za) and click on the CPD button and select April. The article and the questionnaire will appear.

**Reference and Recommended Reading**


3. Guidelines for the Management of Chronic Asthma in Adolescents and Adults. ALLSA Handbook 2010


5. Guidelines for the management of chronic asthma in children 2009 update. ALLSA Handbook 2010


**References and Recommended Reading**


3. Guidelines for the Management of Chronic Asthma in Adolescents, and Adults, ALLSA Handbook 2010


5. Guidelines for the management of chronic asthma in children, 2009 update, ALLSA Handbook 2010


**References and Recommended Reading**


3. Guidelines for the Management of Chronic Asthma in Adolescents, and Adults, ALLSA Handbook 2010


5. Guidelines for the management of chronic asthma in children, 2009 update, ALLSA Handbook 2010


**References and Recommended Reading**


3. Guidelines for the Management of Chronic Asthma in Adolescents, and Adults, ALLSA Handbook 2010


5. Guidelines for the management of chronic asthma in children, 2009 update, ALLSA Handbook 2010


**References and Recommended Reading**


3. Guidelines for the Management of Chronic Asthma in Adolescents, and Adults, ALLSA Handbook 2010


5. Guidelines for the management of chronic asthma in children, 2009 update, ALLSA Handbook 2010


**References and Recommended Reading**


3. Guidelines for the Management of Chronic Asthma in Adolescents, and Adults, ALLSA Handbook 2010


5. Guidelines for the management of chronic asthma in children, 2009 update, ALLSA Handbook 2010

PE in puerperium period of HIV patient

Alexei Ortiz Milan et al, from the Faculty of Medicine at the University of Botswana, recently released a case study, highlighting the management of:

Acute Pulmonary Embolism during Puerperium in an HIV Positive Patient.

Acute Pulmonary Embolism (PE) is a life-threatening condition which results from occlusion of the pulmonary circulation. The most common situation is when a clot travels from the venous system or right side of the heart, diverting the pulmonary blood flow to the left side of the heart without oxygenation. This creates an intrapulmonary shunt which is the cause of hypoxemia.

Acute PE is the most serious clinical presentation of venous thromboembolism.

In a study carried out in the United States between 1995 and 2005, the in-hospital fatality rate of patients with primary or secondary diagnosis of acute PE fell from 12.3–8.2%, and the length of hospital stay also decreased from 9.4 to 8.6 days.

Another study showed significant decrease in-hospital fatality rates both in men and women, from 17.6–10.1% and from 15.6–10.2%, respectively over the 11 years of study period.

"Conclusion from those studies support that acute PE is nowadays less lethal than before and cost for hospitalisation has declined. The reduction in fatality rate of PE can be associated to better screening tool for PE, so allow to recognise earlier those patients with moderate-high clinical probability of PE, and initiating adequate management," says Milan.

Case study

A 37-year-old female on day 23 after a caesarean section with a background of HIV positive on HAART with recent CD4 count 580 mm3, presented to hospital with shortness of breath (SOB) on exertion since delivery. There was no chest pain, no cough and no fever. The patient also had a history of hypertension on treatment (Nifedipine 90 mg+Hydrochlorothiazide 25 mg/ daily), and treatment for pulmonary TB.

On physical exam, no remarkable findings were found. Electrocardiogram was done and it was reported as normal. On admission, she was started on oxygen and antibiotics (Augmentin and Doxycycline) and chest x-ray (CXR) was requested.

Six days after admission she was reassessed by physicians still SOB and now complained of chest pain, palpitations, cough, fever and night sweats. Vital signs were normal. CXR from admission was reported with infiltrations in the right lower zones so cotrimoxazole was started as treatment of pneumocystis carini pneumonia (PCP) and screening for tuberculosis (TB) was initiated. The physician reassessed the following day when the patient had the same symptoms plus left lower limb pain. The notes describe an unwell-looking patient with palour, pulse rate of 113 beat/min, saturating 93% on room air and 98% on oxygen mask, and physical exam revealed a swollen left calf.

The diagnosis of deep venous thrombosis and pulmonary embolism was suspected based on wells score for PE of 75 (78.4% probability of PE), and a left lower limb Doppler ultrasound and Pulmonary Artery Computed Tomography (CTPA) were planned while anticoagulation with Enoxaparin 80 mg twice a day subcutaneously was started. The oral anticoagulant warfarin 5 mg was started; daily INR ordered and the physicians requested close monitoring of Blood Pressure (BP), Respiratory Rate (RR), and Pulse Rate (PR).

CTPA reported band-like intraluminal filling defects in the right pulmonary vasculature consistent with pulmonary embolism and there is consolidation of the posterior-basal segment of the right lower lobe.

The patient continued to deteriorate with a tachypnea of 44/min and oxygen saturations of between 85-90%. Intensive care review was requested due to respiratory distress and desaturating on oxygen to 88-92%. Arterial blood gases showed the following results: pH 7.49, PCO2 36, PaO2, 67, HCO3 26.8.

The patient was transferred to intensive care unit (ICU), intubated and connected to mechanical ventilation on volume assist-control mode and hemodynamic support with noradrenaline was initiated due to severe hypotension. Continuous sedation was given with midazolam and morphine, and anticoagulation continued with enoxaparin and warfarin.

Two days after her admission to ICU, she was successfully weaned from noradrenaline. Nine days after ICU admission extubation trial is performed which failed, and patient reintubated.

Pulmonary embolism is a life-threatening condition associated with high mortality when right ventricular dysfunction is present, anticoagulation and cardiorespiratory supports are the cornerstone of treatment.
and sedation is resumed. Patient remained hemodynamically stable throughout her admission in ICU and did not require vasopressors. Four days after reintubation the patient was successfully extubated and discharged to medical ward. She returned home seven days after ICU discharge.

**Discussion**

Pulmonary emboli are responsible for 10% of all deaths in hospital and are a contributory factor in an additional 10%. In contrast, reports of Venous Thromboembolism (VTE) in patients with HIV infection are sparse. VTE is considered to be ‘provoked’ in the presence of a temporary or reversible risk factor. These factors include surgery, trauma, immobilisation, pregnancy, and oral contraceptive use or hormone replacement therapy and can occur within the last six weeks to three months before diagnosis.

PE may also occur in the absence of any known risk factor. If there are no risk factors then the VTE is considered ‘unprovoked’. VTE is a major cause of maternal mortality. With the risk highest in the third trimester of pregnancy and over the six weeks of the postpartum period. It is up to 60 times higher three months after delivery, compared with the risk in non-pregnant women.

In most patients, PE is suspected on the basis of dyspnoea, chest pain, pre-syncope or syncope, and/or haemoptysis. Once clinical judgment has raised the suspicion of PE, the assessment of clinical probability is to perform through the well validated Wells score.

**Treatment**

Vasopressors may be used to support the blood pressure (BP) when it does not improve with fluid challenge. Norepinephrine appears to improve RV function via a direct positive inotropic effect, while also improving pulmonary vascular alpha-receptor stimulation and the increase in systemic BP. Dobutamine and/or dopamine may be considered for patients with PE, low cardiac index, and normal BP; however, raising the cardiac index above physiological values may aggravate the ventilation-perfusion mismatch by further redistributing flow from (partly) obstructed to unobstructed vessels. Epinephrine combines the beneficial properties of norepinephrine and dobutamine, without the systemic vasodilatory effects of the latter. It may therefore exert beneficial effects in patients with PE and shock.

Anticoagulation, initially parentally with heparin (unfractionated heparin or low molecular weight heparin) over the first five to ten days overlapping with the initiation of oral vitamin k antagonists (e.g. warfarin) at least for three months is recommended and aims to reduce early death and recurrent symptomatic or fatal VTE.

The anticoagulant effect of heparin is usually monitored using the aPTT (activated Partial Thromboplastin Time) to achieve an increment of 2-2.5 times above the control aPTT (pre-treatment), and vitamin k antagonists is monitored through the International Normalised Ratio (INR) to achieve target INR between 2-2.5. Alternatively, one of the new oral anticoagulants (e.g. Dabigatran, endoxaban) can be used. In patients whom presented in shock thrombolysis is recommended.

When mechanical ventilation is required, care should be taken to limit its adverse haemodynamic effects. In particular, the positive intrathoracic pressure induced by mechanical ventilation may reduce venous return and worsen RV failure in patients with massive PE; therefore, positive end-expiratory pressure should be applied with caution.

**Conclusion**

A patient with high clinical probability of PE should go straight for Computed Tomography Pulmonary Angiography in order to rule in this pathology. If cardiorespiratory compromise is present, ventilatory and hemodynamic supports should be given along with anticoagulation.

References available on request.

Pulmonary artery computed tomography showing intraluminal filling defects in the right pulmonary vasculature (A) and consolidation in the posterior-basal segment of the right lower lobe (B).
Our patient is a 47-year-old male who presented to the renal unit with end-stage renal disease in 2005. The aetiology of his kidney disease was unknown at that time although he did have hypertension that was thought to be secondary to his renal failure. The patient had no history of diabetes and was commenced on tegretol for a severe painful peripheral neuropathy that had developed before he required dialysis. He also reported no family history of any chronic illnesses before he was commenced on haemodialysis.

An ultrasound of his kidneys revealed that they were small and shrunken. In 2007 at age 37 he received a live related allograft from his sister who was a year older than him. The donor had no known medical illnesses and was considered suitable by the transplant team. The HLA matching was 4/6 and they both had previous exposure to cytomegalovirus infection.

The induction agent was an interleukin 2 receptor blocker and the patient developed immediate diuresis post-transplant. Maintenance immunosuppression consisted of tacrolimus, mycophenolate mofetil and prednisone.

After one month after the transplant he was admitted with allograft dysfunction. The main consideration was of an acute rejection and a transplant biopsy was done. The light microscopy features were in keeping with an acute cellular rejection (Type II A). However, when the electronic microscopy was done myelin bodies were found and on reappraisal of the histology the features were in keeping with a glycogen storage disease.

These inclusions composed of concentric layers with a periodicity of 3.5 to 5 nm and with an onionskin appearance, are considered a hallmark of glycolipid storage disorders.

The recipient and donor then underwent an enzyme assay and genetic testing to exclude Fabry disease. The donor’s Alpha-galactosidase level: 85.21pmol/spot*20h (normal 160-2000pmol/spot*20h) and the diagnosis was confirmed on molecular genetic testing. The recipient’s Alpha-galactosidase level was 25.88pmol/spot*20h.

(Normal: 160-2000pmol/spot*20h) which was sufficient to confirm the diagnosis in a male patient.

Both patients continue to be followed up in our transplant clinic. The transplant team is in the process of assisting the donor to receive enzyme replacement therapy. Through a combined effort of the transplant team, we were able to get the recipient enrolled onto a international charity programme which initially funded enzyme replacement therapy for Fabry disease from 2010 onwards. He has subsequently obtained health insurance and the enzyme replacement therapy was continued for the past seven years.

His other comorbidities that he developed include dyslipidaemia, a urethral stricture and a benign gastric polyp, all of which have been adequately managed. His peripheral neuropathy also improved on enzyme replacement therapy. He has not suffered any of the dreaded complications of Fabry disease and is symptom free. The graphs represent his proteinuria and renal function.

The patient was commenced on enzyme replacement therapy at a dose of 1mg/kg every two weeks since 2010.

The slide (Figure 1) indicates that there has been approximately 1 ml/min/year decrease in renal function over the past 10 years.

The donor has a creatinine clearance (Figure 2) of 99 ml/min in 2016 and her 24 hour protein...
HAVE YOU SEEN

NEUROCARDIO

renal dysfunction

cardiac dysfunction

stroke

neuropathic pain

DISEASE?

SANOFI GENZYME

Sanofi-Aventis South Africa (Pty) Ltd, Sanofi-Aventis House, 44 on Grand Central Office Park, 2 Bond Street, Grand Central Ext 1, Midrand 1685. Reg.No.: 1996/010381/07
RARE DISEASES

is 0.04 g. An echocardiogram revealed an ejection fraction of 66% and no left ventricular hypertrophy. She has recently developed angiokeratomas and a peripheral neuropathy.

The pedigree analysis (Figure 3) and follow up reveals that the recipient’s brother also suffers from Fabry disease. Both brothers’ children, all daughters, have also been diagnosed. The recipient’s son has been diagnosed as well. The remaining siblings were unaffected. The mother of both patients was found to be the carrier. Three other extended family members have also been diagnosed. The average cohort of family members diagnosed with Fabry disease is around five. Thus far, 10 members of this family have been diagnosed with Fabry disease.

Discussion

Fabry disease is a lysosomal storage disorder. It is the second most prevalent lysosomal storage disorder after Gaucher disease. It is inherited as an X-linked inborn error of the glycosphingolipid metabolic pathway. This is a multisystem progressive disease, which is devastating if untreated.

The disease transmitted by the X chromosome. Daughters, however, can be carriers or be affected. If a female is affected, then 50% of her children manifest disease. Affected sons will show overt manifestation of the disease.

It is a pan-ethnic disorder and the prevalence is underestimated due to incorrect diagnosis or delayed diagnosis. The prevalence of Fabry disease is probably underestimated given incomplete ascertainment and the manifestations of the disease being nonspecific.

The diagnosis is often not considered by clinicians, given the rarity of the disease.

In the Fabry Outcome Survey, the mean delay to correct diagnosis after symptom onset was estimated to be 13.7 and 16.3 years for males and females, respectively.

The symptoms of Fabry disease tend to appear in a predictable order in classically affected males (Figure 4). They begin in childhood or adolescence and include severe neuropathic or limb pain, which may be precipitated by stress, extremes of heat or cold and physical exertion.

Neuropathic symptoms occur in more than 75 percent of patients with a mean age of onset of 10 years. Renal disease occurs before CNS and vascular disease.

The morbidity and eventual mortality is seen either manifesting through renal, cardiac or cerebrovascular disease.

When to suspect Fabry disease:

» Acroparesthesias
» Angiokeratomas
» Hypohidrosis
» Left ventricular hypertrophy of unknown etiology
» Stroke of unknown etiology
» Chronic kidney disease of unknown aetiology
» Multiple renal sinus cysts.
» Family history of premature death.

Commonly mistaken diagnosis

» Rheumatoid arthritis due to pain in the joints and elevated ESR.
» Erythromelalgia associated with painful extremities.
» Raynaud’s syndrome causing pain and sensitivity in the extremities.
» Multiple sclerosis responsible for stroke-like events in the brain stem structures.

Inherited kidney disease is under-diagnosed and not well screened for. Screening the family essential in of those patients who have unexplained renal failure. There is also a need for pre-transplant evaluation for Fabry disease or other inherited kidney disease in unexplained end stage renal disease, especially if a family history is present.

Although Fabry disease is considered ‘rare’, its inheritance, genetics, pathophysiology and systemic manifestations are very well understood. The treatment with enzyme replacement therapy reflects a clear understanding of the disorder and newer therapies being investigated provide a reflection of the vast knowledge surrounding the disease process of this storage disorder.
**PPIs for NSAIDs induced gastropathy**

NSAID induced gastropathy can result from any dose or any frequency intake of NSAID drugs as well as long-term use. These drugs are used to decrease pain and inflammation and are often taken by those diagnosed with osteoarthritis and rheumatoid arthritis or other musculoskeletal conditions. NSAIDs are often prescribed to these individuals, as well as suggested as over the counter (OTC) types of NSAIDs. Because of the easy accessibility of these drugs, the incidence rate of NSAID induced gastropathy is high, especially among individuals who are >60 years. The small and large bowel can also be affected.

NSAID induced gastropathy can result in stomach or duodenal ulcers which may even lead to death. There are thousands of hospitalisations over each year just from symptoms resulting from NSAID use. Though these rates are high, most individuals do not know the risk of these medications and continue to take them. Also, this induced gastropathy goes on asymptotically until it is too late and has caused further damage of the gastrointestinal tract.

NSAIDs are COX-1 inhibitors which suppress the mucous barrier in the gastrointestinal system which can lead to breakdown of the GI tract as well as increase in the acidity of the gastric contents.

The mechanism of action and injury of the NSAIDs is caused by interfering with the arachidonic acid pathway (prostaglandins).

**Gastrointestinal effects of aspirin**

Aspirin is being used as an effective analgesic and anti-inflammatory agent at doses >325 mg daily. At low doses (75-325 mg daily), aspirin is the key antplatelet drug in the pharmacological prevention of cardiovascular diseases. However, topical and systemic effects of aspirin in the gastrointestinal mucosa are associated with mucosal damage in the upper and lower gastrointestinal tract. The risk of upper gastrointestinal bleeding with aspirin is increased with old age, male sex, ulcer history and concomitant medication with NSAIDs, cyclooxygenase 2 selective inhibitors, corticosteroids or other antithrombotic agents. In some patients, the cardiovascular benefits of low-dose aspirin might be overcome by the risk of gastrointestinal complications, but withdrawal of aspirin therapy can precipitate a cardiovascular event. These patients will need concomitant therapy with antisecretory agents, especially PPIs, to reduce the gastrointestinal risk. Eradication of Helicobacter pylori infection might be an additional option in patients with a history of ulcer. Furthermore, there is growing evidence that long-term use of aspirin decreases the risk of colorectal cancer, even at low doses. As aspirin is one of the most prescribed drugs worldwide and its clinical impact is huge, physicians need to consider the benefits and harms for each individual patient in order to maximise the benefits of aspirin.

**Treatment results: RCTs**

Omeprazole, the most extensively studied PPI, has a protective effect against NSAID-related mucosal injury. Not unexpectedly, because of its potent acid-inhibiting property, it prevents DU in patients taking NSAIDs. There is evidence that omeprazole also protects against GU. In a crossover, double-blind RCT, 20 normal volunteers were given aspirin 650 mg q.i.d. with either placebo or omeprazole 40 mg/day for 14 days, with endoscopy before and after each treatment period. Omeprazole significantly decreased aspirin-induced gastric mucosal injury (p < 0.01) by protecting 85% of the subjects from extensive erosions or ulcer, whereas 70% of the subjects developed severe injury (rate 3 or 4 on 0–4 scale) on aspirin and placebo. No duodenal injury was seen in any grade or any subject on omeprazole, whereas 50% on placebo developed erosions and 15% had DU (p < 0.001).

Three large RCTs have been carried out in patients with OA and RA comparing omeprazole with placebo, misoprostol, and ranitidine for the prevention of GU and DU. Overall, omeprazole significantly reduced the total number of NSAID-related ulcers when compared with placebo and ranitidine. It was more effective than misoprostol in preventing DU, and equally so in reducing GU. It should be noted that the lowest effective dose of misoprostol was used in this study, and that most of the overall prevention in NSAID-related ulcer in the placebo-controlled studies was due to a reduction in the numbers of duodenal ulcers.

Recently, esomeprazole has been used in RCTs, as it has superiority to omeprazole, in terms of acid inhibition.

**PPIs for NSAID-associated symptoms and lesions**

A recent review, *Effective and safe proton pump inhibitors for the prevention of NSAID associated gastropathy* published in 2016, showed that PPIs are effective in reducing the risk of NSAID-induced ulceration. The review also highlighted the benefits of PPIs in reducing the risk of NSAID-induced bleeding, particularly in patients with a history of peptic ulcer disease.

**Nonsteroidal anti-inflammatory drugs (NSAIDs)** constitute a well-known group of drugs that are most widely used for a variety of inflammatory conditions and pain. However, their gastrointestinal side effects, hamper their usefulness in many clinical settings.

**Reviewed by**  
**Professor Reid Ally**  
A specialist Gastroenterologist and appointed adjunct Professor of Medicine in 2001. Currently he is the Head of Gastroenterology (Wits) and Chris Hani Baragwanath Hospital and senior lecturer and teacher of diagnostic and interventional endoscopy.
In a nutshell

NSAIDs are an essential part of the therapeutic armamentarium despite their well-characterised GI and CV risk profiles. Physicians should not prescribe NSAIDs before taking a careful history and doing a physical examination. When using NSAIDs, cognisance should be taken of age, comorbidities, cardiovascular risks and benefits, as well as GI risks and protection.

Finally, the appropriateness of an NSAID prescription should be emphasised, i.e., to control inflammation and pain, rather than to control pain alone; only then can we hope to limit the expanding NSAID epidemic.

inhibitor therapy in acid-related diseases - a position paper addressing benefits and potential harms of acid suppression by Carmelo Scarpignato et al., concludes that PPI therapy reduces upper GI symptoms in NSAID users.

Standard dose PPIs are indicated for patients taking non-selective NSAIDs at risk for upper GI complications (bleeding and perforation) and for those given selective cyclooxygenase (COX-2) inhibitors having had an episode of previous GI bleeding.

“in both non-selective and COX-2 selective NSAID users, PPI therapy reduces upper GI symptoms, in particular dyspepsia. However, NSAID induced adverse events in the lower GI tract are not prevented by PPIs,” the review states.

GI adverse effects are the most common and include a wide clinical spectrum ranging from dyspepsia, heartburn, and abdominal discomfort to more serious events such as PU with life-threatening complications, including bleeding and perforation. Since symptoms are not a reliable indicator of mucosal damage, it is important to identify factors that predict the risk of GI events in NSAID users.

“The risk factors for upper GI bleeding (UGIB) associated with NSAID use has been well defined by several studies. Among them, the most important are prior history of complicated ulcer and age. Older age is common in NSAID users and those aged above 65 years carry a risk similar to those with a history of PU. Advancing age increases the risk by about 4% per year, probably because of the presence of other associated risk factors,” Scarpignato says.

The presence of multiple risk factors greatly increases the risk of GI complications. The role of H. pylori infection in patients taking NSAIDs and the potential benefit of eradication on upper GI risk in infected NSAID users has been controversial. However, eradication of associated H. pylori infection is beneficial when starting treatment with NSAIDs or aspirin, especially in the presence of an ulcer history.

An often forgotten risk factor for upper GI complications is represented by drug combinations with NSAIDs. While the role of steroids, antiplatelet drugs, and anticoagulants is long known, the synergistic effect of selective serotonin reuptake inhibitors (SSRIs) has until recently been overlooked.

Over the past 15 years, several epidemiologic studies, summarised by three recent meta-analyses have shown an association between SSRI use and the occurrence of UGIB, and found that this risk is further increased among patients, who concomitantly use NSAIDs and/or hold H. pylori infection while it is lowered by concomitant PPI intake.

The most plausible mechanisms underlying this detrimental effect include a marked decrease in serotonin platelet content, with consequent impairment of platelet aggregation in response to injury and prolongation of bleeding time as well as an increase in gastric acid secretion, with potential ulcerogenic activity.

“GI symptoms usually develop within the first few days of starting a NSAID therapy and can actually occur with the first dose of the drug. Although some studies have suggested that the first two months of treatment represent the period of greatest risk for complications with a relative risk of 4.5 %, available evidence (from both RCTs and observational studies) shows that the risk of GI complications is constant over time, either during short-term or long-term NSAID use,” the study states.

“Therefore, even a short course of NSAID therapy carries a risk of GI complications similar to that of long-term treatment. As a consequence, prevention strategies should be implemented regardless of the duration of therapy, especially in patients with more than one risk factor.”

PPIs effective in prevention and treatment

All RCTs have shown that PPIs are more effective than H2RAs in both preventing and treating gastroduodenal lesions. The reasons underlying the superiority of this class of antisecretory drugs have been clarified by preclinical and clinical pharmacological studies indicating that degree and duration of acid inhibition are both important factors in determining their efficacy in the prevention of NSAID injury.

“They also reduce upper GI symptoms associated with both COX-2 selective and nonselective NSAID use. Due to the long half-life and entero-hepatic circulation of several NSAIDs, a split dose PPI might be useful; there is, however, no evidence for the clinical usefulness of this regimen. COX-2 selective NSAIDs have an improved upper GI safety profile compared to traditional compounds, as extensively shown in endoscopy and clinical outcome studies,” the review suggests.

The evidence is strong, with consistent reductions in events of about 50% in large RCTs, meta-analyses of RCTs, and large observational studies in clinical practice.

“Among patients with a prior ulcer bleed, treatment with a COX-2 inhibitor or an NSAID plus PPI is still associated with a clinically important risk of recurrent ulcer bleed (some 10%). In these patients, the combination of a PPI and a COX-2 inhibitor reduces the risk of upper GI bleeding compared to that of COX-2 inhibitor alone. A very recent network meta-analysis indeed found that this drug combination represents the best strategy to prevent ulcer complications,” Scarpignato states.

References available on request.
With OMEZ, the world’s #1 omeprazole brand¹
**Background facts**

Vitamin D (D2 and D3) is a steroid hormone and is produced in the skin from 7-dehydrocholesterol by sunlight (D2 and D3) or ingested with food from plant origin (D2) or animal origin (D3) or from food fortified with vitamin D.

The vitamin D then needs to be activated, first in the liver to 25(OH) D and then in the kidney to 1a25 (OH)D. Vitamin D acts through a vitamin D receptor (VDR) which is a DNA-binding transcription factor.

All tissues do have the vitamin D receptor. Genome-wide studies have identified a genetic influence on 25(OH)D levels.

Circulating levels of 25(OH)D is the best indicator of whole-body vitamin D status and is used to classify vitamin D status as sufficient or insufficient or deficient.

**Definition of vitamin D deficiency**

Levels < 20ng/ml (50nmol/l) are used to diagnose vitamin D deficiency. Levels between 21-29 as insufficiency, and normal as > 30ng/ml. Worldwide the prevalence of vitamin D deficiency is believed to be between 30-50% and most likely higher in the elderly.

Risk factors known are ageing, physical inactivity, smoking, obesity, housebound (or indoor activity), dark skin (need more sunlight), sunscreens and cover-up, and certain drugs such as glucocorticoids. Not all risk factors are probably known as yet.

**Vitamin D and cardiovascular health**

Atherosclerosis, a complex condition involving many cells and systems, remains the leading cause of heart disease.

A number of well-known risk factors (e.g. Hypertension etc.) accelerate the process of atherosclerosis.

Vitamin D deficiency is regarded as an emerging risk factor for atherosclerosis based on its association in long-term population studies with an increased prevalence of cardiovascular disease and based on plausible mechanistic effects on cardiovascular function.

**Vitamin D and cardiovascular risk factors**

1. Vitamin D deficiency is associated with increased arterial stiffness and endothelial dysfunction as well as an abnormal behaviour of vascular smooth muscle-all involved in the process of atherosclerosis.

2. Vitamin D deficiency is associated with an increase in platelet reactivity in coronary artery disease, a state which is recognised to be associated with increased platelet activity.

3. Vitamin D deficiency leads to an up-regulation of the Renin-Angiotensin-Aldosterone system (RAAS) which leads to hypertension.

4. Vitamin D deficiency leads to insulin resistance and a higher prevalence of diabetes mellitus. A low vitamin D level is also associated with low HDL-cholesterol and increased level of triglycerides which is regarded as highly atherogenic.
Evidence indicates that atherosclerosis is an inflammatory condition. Vitamin D deficiency leads to a state of hyperparathyroidism and inflammation documented by increased levels of C-reactive protein and increased levels of Interleukin-10.

Vitamin D levels were found to be low in mood disorders and depression is currently regarded as an important risk for ischemic heart disease, although this link needs more study.

**Vitamin D deficiency and cardiovascular disease: epidemiological studies**

In many large observational studies, at least 10, it was shown that low vitamin D levels were associated with an increase in cardiovascular disease. Recently two large studies with long-term follow-up were published.

In the Copenhagen City Heart Study, 10 170 men and women were followed for 29 years for heart disease. It was demonstrated that low vitamin D levels were associated with a 64% higher risk for myocardial infarction and a 57% risk of early death. The authors added this study to a meta-analysis which showed a 40% increased risk of heart disease associated with low vitamin D levels.

In the Whitehall study, with 5409 older men followed for 13 years, it was shown that low vitamin D levels were linearly related to an increase in heart disease. They showed that doubling of the vitamin D level was associated with a reduction of 20% in vascular mortality and a reduction of 23% in non-vascular mortality. They also did a meta-analysis of 12 prospective studies which showed that high levels of vitamin D as compared to low levels had a 21% lower vascular mortality and a 28% lower total mortality.

**Vitamin D effects of treatment**

Autier et al. showed in a meta-analysis of 18 randomised controlled trials with a observation period of 5.7 years that vitamin D reduced all-cause mortality by 7% (95%CI:1-13%) but did not impact on myocardial infarction or stroke. In another meta-analysis by Elamin et al. of 51 trials, vitamin D therapy did not reduce death, myocardial infarction, or stroke: R.R 0.96 (95%CI: 0.93-1.00) for mortality.

In a Cochrane meta-analysis of 50 trials, it was shown that all-cause mortality was not reduced by vitamin D: Relative Risk Reduction 3% (95%CI: 0 to 6%). However, vitamin D3 (cholecalciferol) did reduce all-cause mortality by 6% (95%CI: 2 to9%) with number needed-to-treat of 161(95%CI:107-481) while vitamin D2 (ergocalciferol) did not have an effect.

**Future directions**

A major double-blind randomised placebo-controlled trial is underway and has enrolled 25 000 men and women: the VITAL trial (Vitamin D and Omega-3 trial). Participants are to receive 2000IU of vitamin D or placebo and 1 gram per day of fish oil for five years.

There is as yet no randomised trial testing the effect of vitamin D on heart disease in the elderly.

**Conclusions**

1. Vitamin D is often deficient in patients especially in the elderly and in people with myocardial infarction.
2. Vitamin deficiency may contribute to atherosclerosis through several mechanisms.
3. Vitamin D deficiency is common and is linked to an increase in cardiovascular disease worldwide.
4. Although treatment of vitamin D deficiency is relatively easy, there are not enough randomised clinical trials to advise specific treatment in specific dose of vitamin D for the individual patient.
5. Sunlight every day for ten minutes on the arms and legs remains an effective way to increase vitamin D levels.


**Fuelling the BLACK MARKET for ED drugs**

It is a well-known fact that South Africans are, globally, amongst the biggest consumers of male sexual enhancement pills. These counterfeit ED drugs are causing many to put their lives at risk.

It's estimated that one in five South African men suffer from erectile dysfunction and only a fraction seek medical help.

The globalisation of drug manufacturing and the anonymity and ubiquity of the internet are fuelling the traffic in male enhancement pills, and generating a market for the more questionable manufacturers.

A study, published in *JAMA Internal Medicine*, by Pieter Cohen, Assistant Professor of Medicine at Harvard Medical School and a colleague collected some of the lesser known facts about an industry that produces millions of pills - and likely generates tens of millions, if not billions in profits.

Male sexual enhancement pills are considered to be one of the most counterfeited drugs in the world, and South Africans are among the biggest consumers of black market ED drugs.

"Rock Hard" and similar so-called 'natural' supplements for men often contain potentially dangerous drugs - some of which have never been tested on animals, let alone humans.

**Fatal drug interactions**

When used in conjunction with nitrate containing medications, PDE5 inhibitors can cause excessive vasodilation and hypotension, which can result in death. The use of nitrate containing medication is a definite contraindication to prescribing PDE5 inhibitors. Nitrate-containing drugs are commonly used to treat diabetes, heart conditions, hypertension and hypercholesterolaemia.

The conditions these medications are used to treat are often widespread in men who have ED, suggesting that a significant proportion of men using counterfeit male sexual enhancement drugs, are putting their lives at risk. It is advised that clinicians emphasise and explain the dangers of black market drugs to patients and underline the critical aspects of proper treatment.

**Background epidemiology of ED**

ED is defined as the inability to have or sustain an erection adequate for satisfactory sexual activity. It is one of the most common chronic medical disorders in men over the age of 40.

A global study of sexual attitudes and behaviours, targeting an adult population aged 40-80 years across 29 countries, identified early ejaculation and difficulty in achieving and maintaining an erection as the problems most commonly reported by men, affecting 24% and 17%, respectively.

The prevalence and severity of the disorder increases with age; men in their 50s are three times more likely to experience ED than men in their twenties. It is estimated that moderate to complete ED affects 45% of men in their mid-60s, with a further increasing prevalence in older age groups.

**Pathophysiology**

Two-thirds of cases of ED are organic in origin and comorbid conditions should therefore be actively evaluated. Heart and vascular diseases (especially those associated with hyperlipidemia, diabetes, and hypertension) are associated with ED.

The combination of these conditions and aging increases ED risk in older men. Other hormonal and metabolic problems including primary and secondary hypogonadism, hypothyroidism, diabetes mellitus and hypertension are considered as possible causes.

*Rock Hard* for Men in 2012 turned out to contain not only counterfeit Cialis (tadalafil) - but also a diabetes drug that can be deadly if used incorrectly. A similar combination killed more than a dozen men in Asia in 2009.

One Utah company alone produced more than a million pharmaceutically-tainted pills monthly, earning $2 million between 2007 and 2010, according to an indictment issued in one of the few cases brought against such manufacturers.

More than three-quarters of male enhancement supplements tested in one study in Singapore contained pharmaceuticals that were not disclosed - and half of them were present in higher doses than recommended.

Over 45 different versions of drugs in the same class of Viagra have now been found in male sexual supplements. A Dutch study found that 75% of the products sold in the Netherlands contained at least one analogue, or chemical variant that has the same effect as Viagra.

A product called ‘Mojo Nights’ recently analysed by the Food and Drug Administration (FDA) included not just counterfeit Viagra, but also three different analogue drugs.

The FDA identified three tainted supplements: ‘Vicerex’ and ‘Bullet Proof,’ which contain counterfeit Cialis and “Lightning ROD,” which includes an analogue of Viagra.
With 1 in every 2 men over 40 having some degree of Erectile dysfunction (ED),

New Actigra 100 can help you ACT like a TIGER in the bedroom...

REFERENCE:
1. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. Journal of Urology 1994;151:54-61. Location: Massachusetts, USA. Levy J. Available online at: https://www.researchgate.net/publication/14944126_Impotence_and_its_medical_and_psychosocial_correlates_Results_of_the_Massachusetts_Male_Aging_Study

Recipe: 1.5 - Vasodilators - peripheral

ACTIGRA 100 Reg No: 457/1.5/0473. Each tablet contains sildenafil citrate equivalent to 100 mg sildenafil.
chronic renal failure, and hepatic failure, also negatively impact on erectile function. Testosterone levels do decline slightly with age, but are only related to ED in the small minority of men (~3-5%) who are truly hypogonadal and have low hormone levels. Substance abuse, such as excessive intake of alcohol or other recreational drugs is a major contributor to ED.

Smoking, a known cause of arterio-occlusive disease, is clearly a co-factor and probably an independent etiologic factor itself. Penile anatomical defects and Peyronie's disease may contribute to erectile problems. Spinal cord injuries, pelvic and prostate surgery and pelvic trauma are less common causes of dysfunction. Psychogenic disorders, including depression, dysphoria, and anxiety states are associated with an increased incidence of multiple sexual dysfunctions including erectile difficulties.

Latrogenic ED can result from nerve disrupting pelvic or prostate surgery; inadequate glycermic, blood pressure, or lipid control; and many of the medications commonly used in primary care. Antihypertensive medications, notably diuretics and central acting agents, can cause ED, as can digoxin, psychopharmacologic agents, including some of the newer antidepressants, and antitestosterone hormonal agents.

**Investigation**

**Medical history**
The medical history should include review for risk factors and screening for psychological problems. A medication review, including over-the-counter drugs may reveal the source of the problem since medications have been implicated in up to 25% of cases of ED.

Some medications have adverse effects on all phases of sexual functioning, making clarification of the patient's complaint a priority before ascribing symptoms to specific medication side-effects. When evaluating for the presence of psychological problems, brief screening for depression may elicit responses. Other psychiatric conditions, such as anxiety, may also be responsible for ED. It is critical that the social history include assessing for stress regarding a relationship or substance abuse including alcohol and cigarettes. Specific questions regarding the presence of claudication during activity (e.g., walking up stairs) or decreased thigh muscle strength or size increases suspicion for pelvic inflow vascular occlusive disease.

Finally, a review of daily activities and of cardiovascular status are important to determine the potential risk for enhancing ED in patients who may have a sedentary lifestyle and who may be at risk for an adverse cardiac event when sexual activity potential is increased.

**Sexual history**
A sexual history is the most important component of diagnosis. Some physicians may find it useful to use a sexual health questionnaire, and to involve the partner as this will not only confirm the problem, but also may reveal other causes of sexual dysfunction.

**Focused physical examination**
The physical examination should be comprehensive, with emphasis on several areas. Evaluation of blood pressure, cardiac size and heart sounds, and a complete peripheral vascular examination looking specifically for abdominal or femoral bruises, diminished femoral pulses, orthrig muscle wasting (signs of decreased pelvic inflow), may contribute to the diagnosis of vascular disease as an associated cause. A neurologic examination that includes the evaluation of pelvic sensory function and anal sphincter tone is needed to confirm both sympathetic and parasympathetic function.

A digital rectal examination of the prostate should be conducted, and a visual and manual exam of the penis to discover any anatomical defects and help to identify Peyronie's disease. Immature secondary sex characteristics, including lack of male hair distribution, poor penile and testicular development, gynecomastia, and fine wrinkling at the corners of the eyes and mouth, indicate the possibility of hypogonadism.

**Laboratory evaluation**
Laboratory testing to evaluate ED will confirm risk factors/entities previously identified. A urine analysis to rule out renal disease or infection; a complete blood count to note any potential hematologic disorder; a chemistry profile to check for fasting glucose, renal, and hepatic function; a lipid profile to rule out hyperlipidemia; and TSH to evaluate thyroid function.

Prostate specific antigen (PSA) should be considered in men over age 45 years with risk factors for prostate cancer especially if testosterone treatment is a possibility. A morning serum total testosterone and prolactin level should be measured on all patients, although the threshold level of testosterone for maintaining an erection is unknown.

Borderline or unequivocally low levels require confirmation of diagnosis by measuring calculated free or bioavailable testosterone and sex hormone binding globulin (SHBG) levels. SHBG binds 60% of testosterone and often is low or low normal in obesity and many normal men and therefore results in factually low serum total testosterone measurements. Unequivocally low testosterone measurements additionally require measuring luteinising hormone (LH) and prolactin for differential diagnosis. However, the majority

Patients should understand that lifestyle habits that negatively affect the heart and the peripheral vascular system or the nervous system will also negatively affect the penis.
ERECTILE DYSFUNCTION

of causes of ED are not due to low testosterone.

If the patient is well known to the physician and the problem is clearly not related to libido or ejaculatory disorders, and there are other contributing factors that can account for the ED, these tests can be ordered on an individual basis. If there is any evidence of hypogonadism or the dysfunction is particularly consistent at a young age, then further hormone evaluation is obligatory.

Management counselling
Because ED often has a psychological component, patient or couple counselling may help reduce anxiety and overcome the condition. This therapy is sometimes used in combination with other treatments as directed by the practitioner.

Lifestyle modification
Making healthy lifestyle changes may reduce the symptoms of ED and improve general physical health. Patients should understand that lifestyle habits that negatively affect the heart and the peripheral vascular system or the nervous system will also negatively affect the penis.

Recommended lifestyle changes:
» Stop smoking
» Reduce fat and cholesterol in diet
» Increase exercise
» Lose weight if overweight
» Comply with prescribed diabetes and cardiovascular medication regimens
» Reduce stress
Changing medication regimens to remove causative agents is an option when good alternatives are available and/or the clinical situation permits pharmacologic adjustments.

Medication changes must be individualised depending upon the specific clinical circumstances. Specific treatment regimens for ED are varied; they include oral medications, transurethral suppositories, intracavernosal injection, vacuum devices, and surgery.

Oral medications
The most effective and useful drugs available are inhibitors of phosphodiesterase type V, an enzyme present predominantly in the penile smooth muscles and responsible for vasoconstriction.

Currently, sildenafil, tadalafil and vardenafil are marketed. Randomised trials demonstrate that sildenafil is effective in most etiologies of ED with efficacies of up to 80%.

In some groups, i.e., post radical prostatectomy or diabetes, sildenafil may have lower efficacy ranging from 40 to 57%. Lower doses (25mg) of sildenafil may be given to patients who are elderly; have renal or hepatic insufficiency; have spinal cord injury (where there is an increased sensitivity to sildenafil); have moderate to severe coronary vascular insufficiency and not using nitrates; or are taking another drug that is a cytochrome P450 inhibitor.

Note: When used in conjunction with nitrate containing medications, PDE5 inhibitors can cause excessive vasodilation and hypotension, which can result in death. The use of nitrate containing medication is a definite contraindication to prescribing PDE5 inhibitors.

Recent data suggest severe coronary disease may not be a contraindication to PDE5 inhibitors. However, data is limited and caution is strongly advised in these situations.

Intracavernosal injection therapy
Intracavernosal injection therapy can be considered when oral medications appear to be ineffective. This injection is given directly into the corpus cavernosum through the side of the penis. The success rate is high, but problems may include pain, prolonged erections or priapism, and penile fibrosis and plaques.

It is recommended to start with the minimal effective dose and titrate upwards. Spinal cord injury patients often have an exaggerated response and require lower doses. The recommended maximal frequency of usage is three times weekly with 48 hours between dosages. Urologic consultation is recommended for patients in whom this treatment is being considered. Note: Caution should be exercised for patients on anticoagulation medications.

Penile implant surgery is a successful therapy, although it should be reserved for patients who have considered or tried several other treatments. The surgery is irreversible and the normal function of the corpus cavernosa is obliterated. The surgery carries low morbidity and mortality and the satisfaction rate is high. It is a well-established urological procedure.

Indicators for referral
Common indications for referral to a specialist include: significant penile anatomic disease, a younger patient with a history of pelvic or perineal trauma, cases requiring vascular or neurosurgical intervention, complicated endocrinopathies, complicated psychiatric or psychosocial problems.

References available on request.

Substance abuse, such as excessive intake of alcohol or other recreational drugs is a major contributor to ED.
The goal of achieving a seizure-free status in patients is accomplished in more than 60% of patients who require treatment with anticonvulsants. Many patients experience adverse effects from these drugs, however, and some patients have seizures that are refractory to medical therapy.

Epilepsy defined
Epilepsy is a chronic disorder, the hallmark of which is recurrent, unprovoked seizures. Many people with epilepsy have more than one type of seizure and may have other symptoms of neurological problems as well.

Epilepsy is a chronic disorder, the hallmark of which is recurrent, unprovoked seizures. Many people with epilepsy have more than one type of seizure and may have other symptoms of neurological problems as well.

Sometimes EEG testing, clinical history, family history and outlook are similar among a group of people with epilepsy. In these situations, their condition can be defined as a specific epilepsy syndrome.

The human brain is the source of human epilepsy. Although the symptoms of a seizure may affect any part of the body, the electrical events that produce the symptoms occur in the brain. The location of that event, how it spreads and how much of the brain is affected, and how long it lasts all have profound effects. These factors determine the character of a seizure and its impact on the individual. Essentially, anything the brain can do, it can do in the form of a seizure.

Having seizures and epilepsy can affect one's safety, relationships, work, driving and so much more. Public perception and treatment of people with epilepsy are often bigger problems than actual seizures. A person is diagnosed with epilepsy if they have one or more seizures that were not caused by some known and reversible medical condition like alcohol withdrawal or extremely low blood sugar. The seizures in epilepsy may be related to a brain injury or a family tendency, but often the cause is completely unknown. The word epilepsy does not indicate anything about the cause of the person’s seizures or their severity.

Treatment and management
A recent study by David Y Ko, MD Associate Professor of Clinical Neurology, Associate Director, USC Adult Epilepsy Program, Keck School of Medicine of the University of Southern California, highlights the desirability of monotherapy. According to the authors, “Monotherapy is desirable because it decreases the likelihood of adverse effects and avoids drug interactions. In addition, monotherapy may be less expensive than polytherapy, as many of the older anticonvulsant agents have hepatic enzyme-inducing properties that decrease the serum level of the concomitant drug, thereby increasing the required dose of the concomitant drug.”

People with seizures experience psychosocial adjustments after their diagnosis; therefore, social and/or vocational rehabilitation may be needed. Many physicians underestimate the consequences that an epilepsy diagnosis may have on patients.

“For example, patients with epilepsy may live in fear of experiencing the next seizure, and they may be unable to drive or work at heights,” states Ko.

Refer patients with intractable spells to a neurologist or an epileptologist for further workup, including video-electroencephalographic (EEG) monitoring, to characterise the etiology of their seizures. A neurosurgical consult is recommended when the possibility of surgical management is considered.

Recurrence risk
For patients who have had more than one unprovoked seizure, treatment with an anticonvulsant is recommended, states the study.

“However, the standard of care for a single unprovoked seizure is avoidance of typical precipitants (e.g., alcohol, sleep deprivation); anticonvulsants are not recommended unless the patient has risk factors for recurrence.”

The risk of recurrence in the two years after a first unprovoked seizure is 15-70%. Principal factors that increase the risk of recurrence are an abnormal brain magnetic resonance image (MRI) study, an abnormal electroencephalogram (EEG), and a partial-onset seizure.

On brain magnetic resonance imaging (MRI), a focal abnormality in the cortical or limbic regions that indicates a possible substrate
The FINE ART of CONTROL
EPILEPSY / BIPOLAR

Valeptic CR 300 Each controlled release tablet contains sodium valproate 300 mg. Reg. No. 44/2.5/0067.
Valeptic CR 500 Each controlled release tablet contains sodium valproate 500 mg. Reg. No. 44/2.5/0068.

For full prescribing information, refer to the package insert approved by the medicines regulatory authority 1004178 08/2016
Private Bag X69, Bryanston, 2021.
Tel. +27 11 635 0000 www.adcock.com
Epilepsy statistics

- Slightly more men than women have epilepsy.
- 1 in 20 people will have a seizure at some time in their lives.
- Up to 80% of people with epilepsy will be able to control their seizures with medication.
- 75% of people with epilepsy will experience their first seizure before the age of 20.
- Up to 80% of people with epilepsy will be able to control their seizures with medication.
- 1 in 20 people will have a seizure at some time in their lives. However, this does not mean that they have epilepsy (which requires a specific diagnosis).
- Slightly more men than women have epilepsy.

Abnormalities on an EEG may include any of the following:

- Epileptiform discharges
- Focal slowing
- Diffuse background slowing
- Intermittent diffuse intermixed slowing.

Epileptiform abnormalities and focal slowing are the EEG findings associated with the highest risk of seizure recurrence. Nevertheless, even a normal EEG does not eliminate recurrence risk.

The risk of recurrence in a person with one generalised tonic-clonic seizure, a normal EEG, a normal brain MRI, and no evidence of focal onset is about 15%; in this case, the patient is not treated. If a patient has all risk factors, the risk is approximately 80%, and the patient is treated.

“An unresolved question is how to treat patients with one abnormality, whose recurrence risk is 30-50%. One approach is to base the decision on a discussion with the patient that includes the risk of seizure recurrence, the risk of toxic effects from the anticonvulsant, and the benefits of avoiding another seizure.

“The clinician should also describe seizure precautions, including not driving for a specific time. Treatment with anticonvulsants does not alter the natural history of seizure recurrence.

### Active ingredient

<table>
<thead>
<tr>
<th>Active ingredient</th>
<th>Epilepsy/seizure type</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Simple and complex partial seizures, generalised tonic-clonic seizures.</td>
<td>Dose related: Nausea, double vision, unsteadiness. Allergic: Rash, reduced white blood cells count, increased appetite (rarely), no obvious effect on concentration, memory or behaviour.</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>Second or third choice for myoclonic seizures. Effective “add-on” for tonic-clonic and absence seizures. May be used in status epilepticus.</td>
<td>Dose related: Drowsiness, lethargy, drooling and hyperactivity in children. Drug loses effect over time. May cause inflammation of the veins.</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Drug of choice in status epilepticus (rectally or intravenously). Rarely used in regularly in tablet form.</td>
<td>Dose related: Drowsiness, lethargy, drooling and hyperactivity in children.</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>First or second choice for typical absence seizures. May be effective in myoclonic seizures. Not effective in generalised tonic-clonic seizures.</td>
<td>Dose related: Drowsiness, nausea, vomiting, headache, irritability. Allergic: Rashes.</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>‘Add-on’ and (in patients over 12 years) monotherapy in generalised tonic-clonic seizures (possible second choice after sodium valproate). Effective in absences with myoclonic seizures and partial seizures.</td>
<td>Dose related: Sedation, unsteadiness and possibly worsening of seizures. Allergic: Rash may occur in 10% of patients, particularly if sodium valproate is taken simultaneously. To avoid rashes the drug must be introduced very gradually.</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Primary generalised tonic-clonic seizures and partial seizures.</td>
<td>Similar to carbamazepine, but less severe.</td>
</tr>
<tr>
<td>Sodium valproate</td>
<td>First choice in primary generalised tonic-clonic seizures, typical absence, atonic and myoclonic seizures and photosensitive epilepsy. Effective in partial seizures (second choice after carbamazepine).</td>
<td>Dose related: Tremor, sedation, restlessness, increased appetite. Allergic: Stomatitis iridisation, inflammation of liver and pancreas. Chronic use: Hair loss (usually transient), weight gain, low platelets in blood (may cause excessive bleeding), Should not be taken during pregnancy.</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Prescribed for partial seizures with or without secondarily generalised seizures, inadequately controlled by conventional first-line drugs.</td>
<td>Dose related: Drowsiness. Loss of appetite and weight may occur.</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>Similar to sodium valproate</td>
<td>Similar to sodium valproate</td>
</tr>
</tbody>
</table>
reurrence; it only reduces the risk for the duration of treatment.

“The First Seizure Trial Group randomly selected 397 patients with an unprovoked, generalised tonic-clonic first seizure to either receive prophylaxis with a conventional anticonvulsant (i.e., carbamazepine, phenytoin, valproic acid) or to receive no treatment and reported that about 18% of treated patients had seizure recurrence within one year, compared with 39% of untreated patients,” Ko said.

Therefore, patients must be told that anticonvulsants can reduce their risk of having another seizure, but will not eliminate that risk.

Anticonvulsant therapy
The mainstay of seizure treatment is anticonvulsant medication. The drug of choice depends on an accurate diagnosis of the epileptic syndrome, as response to specific anticonvulsants varies among different syndromes. The difference in response probably reflects the different pathophysiologic mechanisms in the various types of seizure and the specific epileptic syndromes. Some anticonvulsants (e.g., lamotrigine, topiramate, valproic acid) have multiple mechanisms of action, and some (e.g., phenytoin, carbamazepine, ethosuximide) have only one known mechanism of action.

Standard treatment for epilepsy
The standard treatment for epilepsy is the regular use of one or more chemical substances called antiepileptic or anti-convulsant drugs/medication. The management of patients with epilepsy is focused on three main goals: controlling seizures, avoiding or minimising treatment side effects, and maintaining or restoring quality of life. The initial treatment of epilepsy is with a single antiseizure drug. With an ever-expanding list of available antiseizure drugs, and no single antiseizure drug that is clearly superior in terms of efficacy or tolerability, clinicians must individualise the choice of antiseizure drug for each patient.

References:
David Y Ko, MD Associate Professor of Clinical Neurology, Associate Director, USC Adult Epilepsy Program, Keck School of Medicine of the University of Southern California
Epilepsy South Africa Foundation: Epilepsy: facts and statistics/Epilepsy medication
Steven Kaceski, MD, Initial treatment of epilepsy in adults.
Data knows I care for others, not what I care about

Data can never tell your whole story. That’s why we take the time to go beyond your data to gain a better understanding of you.

Where others see you as the sum of data, **we see you**.

#MoreThanData

[www.MoreThanData.co.za](http://www.MoreThanData.co.za)