INTERFACE BETWEEN MEDICINE AND PSYCHIATRY – MENTAL HEALTH MULTI-PROFESSIONAL APPROACHES

Highlights from the 5th annual GMPP symposium, 2017

Introduction

The Glynnview Multi-Professional Practice (GMPP) hosts an annual symposium to encourage collaboration and strengthen the bond between psychiatry, other medical specialities and allied health care disciplines.

The fifth annual symposium was held in Johannesburg in July 2017. This is the only multi-professional symposium on mental health in South Africa and those who attended this year's symposium included, among others, intensivists, casualty officers, psychiatrists, general practitioners, physicians, pain specialists, psychologists, social workers and occupational therapists. This year, for the first time, the meeting included parallel sessions with the aim of teaching general practitioners about management of psychiatric conditions in primary care. These practical workshops covered anxiety disorders, neurogenetics and pharmacogenetic testing in general practice, and multidisciplinary management of chronic pain.

A variety of additional topics were covered, including antibiotic resistance, metabolic syndrome in psychiatric patients, dementia, childhood psychology, attention deficit hyperactivity disorder (ADHD), sensory intelligence, Parkinson’s disease and three ethics topics: ethical use of social media by health care practitioners, a practical approach to recommending driving restrictions for people with epilepsy, and the impending Protection of Personal Information (POPI) Act.

KEY MESSAGES

- There is a bidirectional relationship between the metabolic syndrome and psychiatric illness. Many psychiatric medications have the potential to cause and/or to worsen metabolic abnormalities. Patients with psychiatric symptoms require regular assessment and change of medication if necessary.

- Anxiety disorders are the most common psychological disorders and are frequently comorbid with other psychiatric illnesses, including substance use disorder. Anxiety may present with a wide range of psychological and physical symptoms. In patients with anxiety, psychiatric comorbidities are unlikely to improve if the anxiety is not properly managed.

- Chronic pain is most frequently a combination of both nociceptive and neuropathic pain types. It shares a bidirectional relationship with depression and sleep disturbance. Therefore, the management of chronic pain requires a multimodal, multidisciplinary approach and should not be limited to monotherapy with analgesics (for nociceptive pain), antidepressants or antiepileptic medications (for neuropathic pain).
• Analysis of genetic variants associated with responsiveness to different drugs enables individualised prescription to optimise the dose, improve treatment efficacy, shorten the treatment time, improve safety, enhance patient outcomes and potentially save costs associated with ineffective medication or time in hospital.

• People with epilepsy who have been seizure-free for at least one year may safely drive a motor vehicle. Where it is necessary to alert the authorities to epilepsy-related driving restrictions, this remains the responsibility of the patient and not the treating doctor.

• Resistance to antimicrobials is a global crisis that urgently requires implementation of multidisciplinary antibiotic stewardship programmes in all medical facilities. Such programmes would include (but not be limited to) careful attention to rational antibiotic prescribing and decision-making algorithms; staff training; ongoing monitoring of prescribing practices and errors; attention to hand-washing; infection control protocols and constant surveillance of common pathogens and resistance patterns.

---

**Metabolic syndrome in psychiatry**

The metabolic syndrome (MetS) has become a global pandemic. Worldwide, it affects almost one in every four individuals, with significant impact on financial, emotional and psychosocial wellbeing of both affected individuals and their families.

MetS is characterised by five cardinal clinical features, namely: central obesity, elevated blood pressure (BP), hypertriglyceridaemia, low HDL-cholesterol and high fasting glucose. It is associated with insulin resistance and is known to be a pro-atherogenic, pro-inflammatory and pro-thrombotic state.¹ The presence of these risk factors is associated with a two-fold risk of premature death, three-fold increased risk of myocardial infarction or stroke and five-fold increased risk for diabetes mellitus.¹⁻³

MetS has a bidirectional relationship with psychiatric disorders. Depression and anxiety are common among individuals with MetS, and, in comparison with the general population, MetS is two to five times more common among patients with severe long-term psychiatric illnesses (Table 1).³ MetS is estimated to affect up to almost 70% of patients with schizophrenia, 50% of patients with depressive disorder and 27% of patients with bipolar disorder (BD).

The cause of MetS in patients with chronic psychiatric disorders is...
multifactorial, including genetic predisposition, sedentary lifestyle, smoking and excessive alcohol consumption, unhealthy diet, hormonal imbalances involving leptin and cortisol, and side effects of medications. In patients with depression or BD, dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis may contribute to MetS due to elevated cortisol production; glucocorticoid resistance; impaired glucose tolerance and insulin resistance; increased visceral adiposity; dysregulation of the sympathetic nervous system, glucose metabolism and BP regulation; and increased pro-inflammatory cytokine production. Perhaps with the exception of aripiprazole and ziprasidone, most second-generation antipsychotics are directly associated with weight gain and increased incidence of MetS. Tricyclic antidepressants can cause weight gain, insulin resistance and hypertriglyceridaemia and, although selective serotonin re-uptake inhibitors (SSRIs) are often associated with weight loss in the beginning, long-term use of these medications also causes weight gain. The risk of MetS is further compounded by the reduction in body metabolism that occurs in patients with depression. Mood stabilisers, especially sodium valproate and lithium, have been associated with weight gain, insulin resistance and MetS. Combinations of medications that promote MetS increase the risk of metabolic disturbances even further.3

To guide a carefully considered management strategy, including selection of pharmacotherapy and appropriate referral, all patients with psychiatric disturbances should be assessed for metabolic risk at presentation (Table 2), with reassessment at six weeks, three months and one year and at least annually thereafter. After starting pharmacotherapy, an increase in body weight of more than 7% should prompt consideration of changing to alternative psychotropic medication.

Management of MetS is dependent on the individual metabolic parameters that are impaired. It may include pharmacotherapy for hypertension, dyslipidaemia, diabetes and weight loss. Metformin may be helpful in combination with psychotropic medication, because it is generally well tolerated, improves insulin sensitivity and facilitates moderate weight loss. Other drugs that may be associated with weight loss in appropriate patients include glucagon-like peptide 1 (GLP-1) analogues, topiramate and buproprion/naltrexone combination therapy. Care should be taken to avoid potential drug interactions, where, for example, the use of angiotensin-converting enzyme inhibitors may increase the risk of lithium toxicity and SSRIs may increase the risk of bleeding in patients taking warfarin.3

Table 1. Psychiatric disorders associated with an increased risk of MetS

- Schizophrenia
- Depression
- Bipolar disorder
- Post-traumatic stress disorder
- Binge eating disorder
- Borderline personality disorder
- Substance use disorder (excessive alcohol consumption)

Table 2. Assessment for MetS in patients with psychiatric illnesses

1. History: cardiovascular disease, family history, habits, exercise, diet.
2. Examination: BP, weight, waist circumference, body mass index.
3. Laboratory tests: fasting plasma glucose, lipogram, liver function tests.
4. Psychoeducation: smoking cessation, diet, physical activity, compliance with medication.
5. The cardiometabolic risk profile of each drug needs to be assessed prior to prescription. Choice of psychotropic medication based on cardiometabolic risk profile.
6. Refer as necessary based on results (e.g. physician, dietician, weight management specialist, biokinetist/specialised fitness trainer; relevant social support or wellness groups).
Anxiety disorders

Although anxiety is a functional adaptive emotion, when it is excessive and interferes with normal functioning it becomes detrimental to health and wellbeing. Anxiety disorders are the most common of the psychological disorders, occurring in all ages, with a mean incidence of approximately 18% and a lifetime prevalence of almost 30%. Anxiety disorder frequently begins early in life and is most often (in more than 90% of cases) comorbid with other psychiatric conditions. Importantly, it is one of the most important risk factors for acute postoperative pain and major depressive disorder. Anxiety is prevalent in all patients with substance use disorder, including those who excessively use alcohol. Consequently, if these conditions are to respond to treatment, it is essential to concurrently manage comorbid anxiety.

Anxiety manifests as a wide spectrum of emotional and physical symptoms (Table 3), the most common of which are worrying, counting, checking, washing, perfectionism and social anxiety. In children, the presentation may be atypical, for example, where anxiety manifests as recurrent abdominal pain.5

During a panic attack, hyperventilation causes a respiratory alkalosis. This is associated with a reduction in extracellular calcium concentration that can cause muscle spasms and pain (e.g. chest pain), numbness, clumsiness, blurred vision, derealisation, and a vicious circle of worsening symptoms.

The pathology of chronic stress and anxiety involves a complex interplay between the serotonergic and noradrenergic tracts of the limbic system (regulating behaviour, motivation and emotion), the prefrontal cortex (rational decision-making) and the HPA axis (stress response). Chronic stress, including that related to depressive episodes, may cause structural and functional changes in these areas of the brain leading to disruption of normal homeostatic mechanisms. It is also associated with dysregulation of the immune system. Chronic adrenal stimulation causes an increase in both cortisol and catecholamine production, and is associated with, paradoxically, both a decrease in normal immune function and an abnormal inflammatory response, in both the central nervous system (CNS) and in the periphery. This immune dysregulation contributes to accelerated atherosclerosis, hypertension, dyslipidaemia, MetS and type 2 diabetes, obesity and an increased incidence of cardiovascular events, infections and cancer.6,7 In the CNS, chronic inflammation may alter expression of growth factors, including brain-derived neurotrophic factor (BDNF), and this, at least in part, may explain some of the structural changes that can be observed with imaging studies in patients with depression and other psychological disorders. Furthermore, chronic stress is associated, in a bidirectional relationship, with an increased incidence of sleep disorders, chronic pain and depression.8, 9

Table 3. Symptoms of anxiety

<table>
<thead>
<tr>
<th>Emotional</th>
<th>Physical</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Tearfulness</td>
<td>• Blurred vision</td>
</tr>
<tr>
<td>• Indecision</td>
<td>• Agitation</td>
</tr>
<tr>
<td>• Loss of confidence</td>
<td>• Light-headedness</td>
</tr>
<tr>
<td>• Poor concentration</td>
<td>• Parasthesias</td>
</tr>
<tr>
<td>• Irrational fears</td>
<td>• Muscle weakness</td>
</tr>
<tr>
<td>• Feelings of guilt, sorrow, disgrace</td>
<td>• Short-term memory loss</td>
</tr>
<tr>
<td>• Feeling overwhelmed</td>
<td>• Derealisation</td>
</tr>
<tr>
<td>• Perfectionism</td>
<td>• Depersonalisation</td>
</tr>
<tr>
<td>• Feeling worse in the morning (associated with physiological cortisol peak)</td>
<td>• Changes in appetite</td>
</tr>
<tr>
<td></td>
<td>• Diarrhoea</td>
</tr>
<tr>
<td></td>
<td>• Stomach churning; knots</td>
</tr>
<tr>
<td></td>
<td>• Frequent need to use the toilet</td>
</tr>
<tr>
<td></td>
<td>• Chronic fatigue</td>
</tr>
<tr>
<td></td>
<td>• General body pains</td>
</tr>
<tr>
<td></td>
<td>• Feeling faint</td>
</tr>
<tr>
<td></td>
<td>• Muscle tension/ twitches</td>
</tr>
<tr>
<td></td>
<td>• Increased infections</td>
</tr>
<tr>
<td></td>
<td>• Sexual dysfunction</td>
</tr>
</tbody>
</table>
Antidepressants can be extremely effective for treating anxiety disorders and different patients will respond to varying degrees to different drugs or classes of drugs, in part, dependent on the presence of other psychological comorbidities. The benefit of antidepressants is that they are non-addictive and effective for both anxiety and comorbidities. Furthermore, studies indicate that a therapeutic response is positively associated with neuroplastic changes in the brain with improvement in neurotrophic factors (e.g. BDNF) and return towards normal structure and function.

Choice of drug should be tailored to the individual, concomitant comorbidities and co-prescribed pharmacotherapies. Most antidepressant drugs carry significant risks of drug-drug interactions and side effects that may require reassurance, management or a switch to an alternative agent. However, most side effects are transient and usually resolve within the first week. Initial doses should be low, with slow upward titration according to response. Approximately three-quarters of patients will respond within two weeks and 85% within three weeks. Patients who have not responded to appropriate doses of treatment by four weeks should be switched to an alternative antidepressant. Patient education is important, so that they are empowered to take ownership of both their illness and treatment, with an understanding of how to correctly use their treatment and realistic expectations of what to expect in terms of response and time frames for that. To avoid relapse, pharmacotherapy is required for at least a year before considering careful tapered withdrawal. If symptoms return after withdrawal, treatment should be restarted.

Pharmacological treatment for anxiety is predominantly aimed at the noradrenergic and serotonergic pathways in the CNS. In contrast, drugs that increase dopamine (e.g. sulpiride, bupropion) can worsen symptoms of anxiety. Mainstays of treatment include tricyclic antidepressants (TCAs), SSRIs and seroton noradrenalin reuptake inhibitors (SNRIs). Especially in higher doses, the TCAs have potential for a lot of side effects. However, especially where there are panic episodes, amitriptyline is effective and may also improve symptoms associated with muscle spasm. The SSRIs are the drugs of choice. Paroxetine, sertraline and fluvoxamine are particularly efficacious in anxiety, and fluvoxamine may also be helpful in children with obsessive compulsive disorder. Interindividual response varies, and patients who do not respond to one SSRI may respond better to another. In patients with depression, where anxiety does not respond within a reasonable time frame, depressive symptoms are also unlikely to respond and treatment should be changed. Weight gain may be an important side effect of some SSRIs and may necessitate a switch to alternative therapy.

**SNRIs are more activating than SSRIs**

Duloxetine may also be helpful in chronic pain states. Although better tolerated than venlafaxine, desvenlafaxine may be less effective for symptoms of anxiety. Agomelatine can increase BDNF and may be effective in some patients.

Mirtazapine is a noradrenergic and specific serotonergic antidepressant (NaSSA) that may be effective in low doses. It blocks the α2-adrenergic negative feedback loop on the pre-synaptic nerve end, thereby enhancing norepinephrine and serotonin release. Second-line treatments that may be appropriate for some patients with severe anxiety include low-dose first- and second-generation antipsychotics, short courses of low-dose benzodiazepines, and, in resistant anxiety, anti-epileptic drugs.

Of course, medication is only one aspect of anxiety management. Patients require assistance to improve their coping skills and self-efficacy and to make other positive changes to their lifestyle. This includes encouragement of healthy dietary habits (including sufficient intake of fruit and vegetables), regular physical activity, stress management (including breathing techniques), mindfulness and psychological support.
Stress and burnout in medical professionals

In the workplace, chronic stress and long-term exposure to situations that are emotionally draining may culminate in burnout – a syndrome of physical, mental and emotional exhaustion. Due to the nature of their work, which centres around the psychological, social and physical problems of others and an environment in which there are commonly emotions of anger, embarrassment, fear, despair, grief, anxiety and depression, in conjunction with long working hours, health care professionals are especially at risk. It is estimated that, depending on specialty, the prevalence of burnout symptoms may be as high as 50-90% among doctors, being higher among surgeons (89%) and psychiatrists (70%) and lower in family medicine (50%) and pathology (46%).

In an Australian study, the incidence of burnout during the intern year was 56%.

The gold standard measure of burnout is the Maslach Burnout Inventory, which groups and measures symptoms in three domains:

1. Emotional exhaustion, in which the health care worker feels that they are no longer able to give of themselves at a psychological level.
2. Depersonalisation, in which there are negative, cynical and dehumanising attitudes and feelings towards one’s clients.
3. Feelings of reduced personal accomplishment, with a tendency to evaluate oneself negatively, especially in the context of work, and feelings of unhappiness and dissatisfaction.

The consequences of burnout are significant. It may lead to deterioration in quality of care and is associated with absenteeism and low morale. On a personal level, the individual suffering from burnout is more likely to experience psychological morbidities (e.g. anxiety and depression), physical exhaustion, low self-efficacy, insomnia, increased use of alcohol and drugs, and marital and family problems. The development of burnout may be slow and insidious, with enthusiasm giving way to stagnation (feelings of personal discontent), frustration (less tolerant and empathetic) and ultimately apathy and depression.

Some causes of burnout among medical professions and protective factors are listed in Table 4.

Table 4. Burnout among medical professionals

<table>
<thead>
<tr>
<th>Precipitating factors</th>
<th>Protective and preventative factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Lack of control</td>
<td>1. Lifestyle:</td>
</tr>
<tr>
<td></td>
<td>• personal balance</td>
</tr>
<tr>
<td></td>
<td>• exercise</td>
</tr>
<tr>
<td></td>
<td>• sleep</td>
</tr>
<tr>
<td></td>
<td>• diet</td>
</tr>
<tr>
<td>2. Unclear job expectations – uncertainty of degree of authority</td>
<td>2. Academic work</td>
</tr>
<tr>
<td>3. Feeling undermined, bullied</td>
<td>3. Teaching</td>
</tr>
<tr>
<td>4. Conflict between personal values, ethics and work values</td>
<td>4. Professional accomplishment</td>
</tr>
<tr>
<td>5. Limited resources</td>
<td>5. Employee wellness programmes</td>
</tr>
<tr>
<td>6. High work demands</td>
<td>6. Stress management and improvement of coping styles; mindfulness</td>
</tr>
<tr>
<td>7. Administrative demands (e.g. motivations, forms, record maintenance)</td>
<td>7. Taking time for oneself</td>
</tr>
<tr>
<td>8. Difficulty in maintaining a work-life balance</td>
<td>8. Hobbies outside of work</td>
</tr>
<tr>
<td></td>
<td>9. Time with family and pets</td>
</tr>
</tbody>
</table>
Fresh insights into Parkinson’s disease

Parkinson’s disease (PD) is a progressive neurodegenerative condition with insidious onset, and is the cause of considerable morbidity and reduced life expectancy. Although it is frequently regarded as purely a disorder of movement, this perception is incorrect and in many patients non-motor symptoms predominate (Table 5).

The aetiology of PD is likely to involve an interplay between genetic vulnerability and environmental factors, which may include toxins, pesticides, brain microtrauma and focal cerebrovascular damage. The neuropathology of PD is characterised by selective loss of dopaminergic neurons in the substantia nigra pars compacta with formation of Lewy bodies consequent on the accumulation of alpha-synuclein inside cells. However, research has demonstrated that the pathology in PD is not limited to merely a local structural change or loss of dopamine. There is also widespread involvement of other (non-dopaminergic) structures in the CNS and peripheral tissues, and PD-related neurodegeneration is likely to occur several decades before the onset of motor symptoms.

In the CNS, the formation of Lewy bodies is progressive, spreading from the rostral to upper brainstem and then to other brain areas, including the limbic system and frontal lobes. This progressive spreading pattern, along with the presence of Lewy-type alpha-synucleinopathy in the spinal cord and peripheral tissues, is responsible for appearance of non-motor symptoms (e.g. constipation, anxiety) years before the development of motor symptoms and dementia.13,14

In addition to alpha-synuclein deposition, there are other pathophysiological mechanisms that have been shown to contribute to the pathophysiology of PD and which might represent novel targets for treatment in the future. These include oxidative damage; neuroinflammation and microglial activation; intracellular accumulation of other insoluble proteins; tau and amyloid formation; and growing evidence that alpha-synuclein may behave in a prion-like manner.13-15

Diagnosis

Diagnosis of PD is made on clinical examination and requires identification of three cardinal motor manifestations of Parkinsonism (bradykinesia plus rest tremor and/or rigidity) and three further categories of diagnostic features (supportive criteria, red flags and exclusion criteria) that establish PD as the cause. However, although motor symptoms remain the core clinical feature of Parkinsonism, increasing recognition is being given to the non-motor symptoms, which occur in almost all people with PD and often precede the motor symptoms.12,16 Timeous identification and management of these symptoms is essential to reduce associated morbidity. Radiological tests may be useful to support the diagnosis and to exclude other causes of symptoms, but are not reliable enough to make a diagnosis of PD.

Table 5. Non-motor symptom subtypes in PD12

<table>
<thead>
<tr>
<th>Brainstem phenotype</th>
<th>Limbic phenotype</th>
<th>Cortical phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Excessive daytime sleepiness</td>
<td>a) Anxiety</td>
<td>a) Dementia</td>
</tr>
<tr>
<td>b) REM sleep behaviour disorder</td>
<td>b) Anxiety/depression</td>
<td>b) Amnestic</td>
</tr>
<tr>
<td>2. Autonomic dominant</td>
<td>2. Fatigue dominant</td>
<td>c) Mild cognitive impairment</td>
</tr>
<tr>
<td>a) Gastrointestinal</td>
<td>3. Pain dominant</td>
<td>d) Apathy</td>
</tr>
<tr>
<td>b) Genitourinary</td>
<td>4. Weight loss phenotype</td>
<td></td>
</tr>
<tr>
<td>c) Adrenergic (postural and other hypertension)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Prognostic prediction

Currently, because of the heterogeneous nature of the pathophysiology and clinical presentation of PD, there is no clear method by which to predict progression and with which to develop more personalized care approaches in clinical practice using baseline clinical information. However, a recent study classified patients into one of three groups according to composite motor score and the presence of three non-motor symptoms (cognitive impairment, REM sleep behaviour disorder and dysautonomia). In comparison to patients with only motor symptoms, those with motor and non-motor symptoms had the lowest level of cerebrospinal fluid (CSF) amyloid-β and amyloid-β/total tau ratio, a greater degree of brain atrophy and a greater decline in motor and cognitive deficits over a three-year follow-up period.17

Treatment of PD

Levodopa (L-dopa) is the most efficacious and best tolerated pharmacological treatment for PD and remains the gold standard. However, its utility is limited by lack of 24-hour symptom control (‘on’ and ‘off’ periods), fluctuations in response and the development of motor complications (dyskinesia) at high doses and with long-term use.

A number of novel treatments have been developed to address the shortcomings of L-dopa (Table 6). Rasagiline increases ‘on’ time with fewer side effects than L-dopa and is helpful especially in early PD. It may also be useful in in combination with L-dopa in patients with more advanced disease and symptom fluctuations, especially in terms of freezing and gait disturbances, motor symptoms, mood symptoms and impaired bladder control. Apomorphine injection is quick acting and very effective. It works immediately and may be very useful as a rescue therapy for episodes of ‘off’.

<table>
<thead>
<tr>
<th>Table 6. Management considerations for patients with PD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Management strategy</strong></td>
</tr>
</tbody>
</table>
| Increase ‘on’ time | • Novel slow-release L-dopa preparations  
• Mono-B inhibitors: Rasagiline  
• COMT (catechol-O-methyl transferase) inhibitors: opicapone, entacapone  
• Long-acting dopamine agonists |
| Improved gastrointestinal function | Dysphagia, gastritis, delayed gastric emptying, small intestine bacterial overgrowth |
| Non-oral therapies | Apomorphine  
Intestinal L-dopa gel  
L-dopa subcutaneous infusions  
Deep brain stimulation |
| Control of non-motor symptoms | Depression, apathy, anxiety, dementia, psychosis, constipation, orthostatic hypotension, sialorrhoea, fatigue, insomnia, excessive daytime sleepiness, bladder control, erectile dysfunction, pain |
Mechanisms worsening chronic pain, including psychological factors

Chronic pain is strongly associated with psychiatric comorbidities, particularly anxiety, depression and insomnia. Accordingly, pain is associated with decrements of many aspects of patients’ lives including physical and emotional functioning, affective symptoms and sleep problems. The negative impact is higher in patients with greater pain severity. However, there is a bidirectional relationship between chronic pain and these symptoms. Patients with somatisation, health-seeking behaviours and poor sleep are at high risk of developing chronic widespread pain. The risk increases in tandem with severity of anxiety, depression or sleep problems, and those with multiple predisposing factors are at the highest risk.

Both the peripheral nervous system and CNS are capable of considerable neuroplasticity. Structural and functional alterations occur consequent to depression, anxiety and pain, but these changes may also be reversed by appropriate treatment. Synthesis of BDNF and other neurotrophic factors that are essential to cell health and growth, as well as apoptosis, and which are important for normal CNS function, learning and memory, is reduced in anxiety, depression and pain states and during times of stress. Conversely, antidepressant treatment (and exercise) is associated with increased expression of BDNF in the limbic system, which is responsible for mood.

The HPA is under direct control of various brain pathways, including the hippocampus (which exerts an inhibitory influence on hypothalamic corticotropin-releasing factor (CRF)-containing neurons) and the amygdala (which exerts a direct excitatory influence on hypothalamic CRF-containing neurons), and which also receive feedback from the HPA via glucocorticoids and monoamines. Under conditions of prolonged severe stress and also in depression, sustained elevations of glucocorticoids cause damage to hippocampal neurons and reduce neurogenesis, leading to excessive activation of the HPA axis in some patients. Furthermore, these changes also lead to activation of immune cells, with a resultant increase in release of proinflammatory cytokines and systemic inflammatory activity. These affect the brain in a number of ways, including altered metabolism of serotonin and dopamine; activation of CRF, which further increases glucocorticoid activity; increased glutamate release and excitotoxicity, with resultant neuronal cell death and demyelination; and reduction in modulating growth factors, such as BDNF. Interestingly, adjunctive anti-inflammatory treatment, in particular celecoxib, has antidepressant effects with and without concomitant antidepressant medication. Add-on celecoxib was associated with improved rates of both response and remission.

The amygdala has a dual facilitatory and inhibitory role in modulation of pain, behaviour and nociceptive processing. Negative affective states that correlate with increased amygdala activity, such as stress, depression and anxiety, activate pain-facilitating pathways and enhance the pain response.

This has important clinical correlations. For example, two of the most significant predictors of postoperative pain are preoperative pain and anxiety. Psychological stress is a significant predictor of analgesic consumption, and greater baseline pain and anxiety predict slower recovery from pain and greater likelihood of ongoing chronic pain after surgery. In contrast, careful pre-emptive analgesia and management of preoperative anxiety improve postoperative outcomes.

Pain itself may be classified according to its pathological origin:

- Nociceptive pain, consequent on stimulation of peripheral nociceptors;
- Neuropathic pain, arising from a lesion in the CNS (brain or spinal cord);
- Central sensitisation or dysfunctional pain, arising consequent on hypersensitivity of the pain system (amplification of sensory neural signalling) within the CNS such that normally innocuous stimuli are associated with exaggerated prolonged and widespread pain. Central sensitisation plays an important role in the pain associated with fibromyalgia, osteoarthritis, musculoskeletal disorders with generalised pain hypersensitivity, headache, temporomandibular joint disorders, dental...
pain, neuropathic pain, visceral pain hypersensitivity disorders and postsurgical pain. However, in many patients, and especially those with chronic pain, the pathophysiology is mixed, involving peripheral and central mechanisms common to both nociceptive and neuropathic pain types. Prolonged or inappropriately managed acute nociceptive pain may lead to sensitisation of the peripheral nervous system (dorsal root ganglion) and CNS, with hyperexcitability, functional reorganisation of pain centres in the brain, and changes in the balance of pain impulse facilitation/inhibition in descending pain pathways. This leads to loss of inhibitory control in the spinal cord (disinhibition), which results in ongoing chronic pain.

Because of the multiple pathways and areas of both the peripheral and CNS involved in chronic pain and the interactions between pain, psychiatric symptoms and sleep, effective management requires a multidisciplinary biopsychosocial approach that considers both physical and emotional factors (Table 7) and carefully considered polypharmacy. Treatment goals include balancing efficacy, safety and tolerability, reducing baseline pain and exacerbations, improving function and quality of life and rehabilitating the nervous system.

### Table 7. Multidisciplinary management of chronic pain

<table>
<thead>
<tr>
<th>Pharmacotherapy</th>
<th>Stress management</th>
<th>Biofeedback</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep hygiene</td>
<td>Physical and/or occupational therapy</td>
<td>Intervventional procedures</td>
</tr>
<tr>
<td>Lifestyle management</td>
<td>Education</td>
<td>Complementary therapy</td>
</tr>
</tbody>
</table>

**Figure 1. Mechanism-based pharmacological treatment for chronic neuropathic pain**

Adapted from references 22-28. Image from: https://www.slideshare.net/ragsamkhamoh/diabetic-p-neuropathy

**Medications affecting peripheral sensitisation:**
- Capsaicin
- Local anaesthetics
- TCAs
- NSAID’s

**Medications affecting descending modulation:**
- SNRIs
- TCAs
- Tramadol, opioids

**Medications affecting central sensitisation:**
- α2δ ligands
- TCAs
- Tramadol, opioids

TCA: Tricyclic antidepressant; NSAID: Nonsteroidal anti-inflammatory drug; SNRI: Serotonin noradrenaline re-uptake inhibitor (venlafaxine, duloxetine); α2δ-ligand (pregabalin, gabapentin)
Nonpharmacological management may include transcutaneous electrical nerve stimulation (TENS), therapeutic massage, mindfulness, meditation and relaxation, acupuncture, cognitive behavioural therapy and guided imagery. Pharmacological options depend on the likely origin of pain with consideration of psychological and physical comorbidities (Figure 1). In chronic and severe pain, the initial pain management strategy should be commensurate with the level of pain, starting with effective doses and combinations of medications and stepping down (if possible) as pain and function improve. Expectations and goals of therapy should be carefully discussed with the patient. In chronic pain, total pain relief is unlikely and more realistic goals are >30% pain relief and improvement in function and quality of life. Patients in whom pharmacotherapy and other conservative modalities are unsuccessful may benefit from referral for an appropriate nerve block or other interventional procedure (e.g. adhesiolysis, spinal cord stimulator, medication pump).

**Driving restrictions in people with epilepsy**

Driving a motor vehicle is a dangerous activity. Naturally, there is concern that people at risk of seizures or alteration in or loss of consciousness may be at increased risk for accidents. Conversely, restricting driving among people with epilepsy has a considerable impact on their livelihood, daily activities and quality of life, e.g. taking the children to school, driving to work, to the shops or for social or leisure engagements.

Nevertheless, approximately 60% of people with epilepsy have a driver’s license, equating to around 700 000 commuters on the road.

Despite this, it is estimated that only 0.1-1% of all accidents may be due to an epileptic event. This is in stark contrast to the high percentage of accidents caused by alcohol. In 2015, the World Health Organization reported that 58% of South African road traffic deaths involved alcohol. Furthermore, seizure-related motor vehicle accidents may be disproportionately reported, because the person with epilepsy is more likely to require admission to the emergency room following a seizure than a healthy, uninjured driver.

In fact, it has been suggested that people with epilepsy may be at lower risk of road accidents than many other subpopulations of drivers, because they are more aware and usually avoid driving unless their seizures are controlled with medication. They may also drive more cautiously and avoid peak hours and busy roads.

Nevertheless, a driving restriction policy is necessary that balances the safety of the person with epilepsy and other road users against the restrictions on the patient’s opportunities for a normal life. Based on the observation that the best indicator of seizure risk is the interval from the most recent seizure, the following guidelines are recommended:

1. A person with epilepsy may be qualified to drive if they have been seizure-free for >1 year.
2. If seizures only occur during sleep, then the risk of a seizure during wakefulness is lower and the seizure-free period to qualify for driving may be reduced to six months.
3. Less stringent restrictions may also be appropriate for patients in whom level of consciousness is not reduced to the point where reactions and behaviour are compromised (e.g. partial seizures).
4. Between 60% and 70% of people with epilepsy will achieve remission from seizures allowing tapering and trial of therapy discontinuation. This may be appropriate where patients are seizure-free for at least two years and there are no other signs of pathology (e.g. no epileptiform activity on ECG, normal imaging studies). Under these circumstances driving should be restricted for three months.
5. Drivers with epilepsy must be compliant with medication and follow-up health care visits.
6. Where it is necessary to alert the authorities to epilepsy-related driving restrictions, this remains the responsibility of the patient and not the treating doctor.

**Dr Johan Smuts**
Neurologist
Pretoria
Clinical applications of genetic testing

Genetic polymorphisms are responsible for considerable interindividual variation in not only disease risk, but also response to preventative and therapeutic strategies. Genetic testing can provide information about risk for specific diseases; metabolism of fats, carbohydrates, hormones, toxins and drugs; obesity risk and resistance to weight loss; and exercise physiology, in terms of requirements for weight loss, endurance and power potential, injury and recovery risk. The results of these tests may facilitate a personalised approach to patient management, guiding decisions about which lifestyle modifications (including diet, exercise and nutritional supplementation) would be most beneficial and realistic expectations from those, as well as providing information about the likely efficacy and safety of potential pharmacotherapies.

Individual variation in drug metabolism is an important factor that affects response to drug therapy and the potential for side effects and drug-drug interactions. Analysis of genetic variants associated with responsiveness to different drugs enables individualised prescription to optimise the dose, improve treatment efficacy, shorten the treatment time, improve safety, enhance patient outcomes and potentially save costs associated with ineffective medication or time in hospital. Patients who are likely to benefit from pharmacogenetic testing include those who are starting new medication, those who are not responding to or who are experiencing side effects from existing therapy, and those who require doses outside of the recommended range.

Some examples of tests for genetic variants include the following:
• Cytochrome P450 (CYP450) 2D6 is responsible for oxidative metabolism of up to 25% of prescribed medications, including antidepressants, antipsychotics, opioids, anti-arrhythmics and tamoxifen, many of which have a narrow therapeutic window. Up to 10% of Caucasians carry genetic alleles responsible for absent enzymatic activity and are poor metabolisers. These individuals have increased risk of toxicity associated with numerous drugs, including desipramine, venlafaxine, amitriptyline, haloperidol, codeine, tramadol, oxycodone, metoprolol, timolol, carvedilol and propafenone. Conversely, the ultra-rapid metaboliser phenotype is associated with a poor response to antidepressant therapy.
• Polymorphisms in CYP 2C19 and 2C9 have been associated with reduced efficacy or dosing complications associated with (among others) clopidogrel, imipramine, sertraline, warfarin, NSAIDs and phenytoin.
• ABCG2 and SLCO181 polymorphisms influence statin plasma levels and may be helpful to predict risk of statin-associated myalgia and myopathy.
• The VKORC1 genotype predicts response to warfarin and may assist in dosing.

The mygeneRx DNA test analyses 62 genetic variations within 20 genes and is able to provide accurate and actionable recommendations for over 200 different prescription drugs, including cardiovascular, antimetabolite, anti-infective, cardiovascular, psychiatric, neurotropic and pain medications within 35 different drug classes. The full screen costs R3500 and has a number needed to treat (NNT) of 6.5.

More information about mygeneRx can be found at www.dnalysis.co.za.
Antimicrobial resistance: The Achilles heel of our time

Antibiotic resistance is a global crisis. The problem of increasing resistance among both Gram-negative and Gram-positive organisms is exacerbated by the dearth of research into, and development of, novel antibiotics and is set to sabotage other technological advances in medicine, as sepsis caused by resistant organisms is likely to become overwhelming. It is estimated that, if left unchecked, infections caused by antibiotic-resistant organisms will be responsible for more than 300 million deaths by the year 2050.

In South Africa, even in advanced medical units with strict antibiotic stewardship protocols, antibiotic resistance is common, especially among Gram-negative organisms, such as Klebsiella and Pseudomonas. The reported incidence of multidrug-resistant (MDR) tuberculosis doubled in the period 2007-2014 to more than 14 000 cases, with a current prevalence of approximately 3%. Extremely drug-resistant (XDR) tuberculosis, for which there is no treatment, has been reported in more than 100 countries, including South Africa. Treatment resistance is also increasing among Candida and other fungal species, HIV, Plasmodium and influenza pathogens.

A multitude of genetically coded mechanisms accounts for resistance to different antimicrobials. These include drug inactivation, active efflux, modification to drug targets and decreased cell permeability. The rapid growth of microorganisms facilitates rapid adaptation due to selection pressures, and genes for antimicrobial resistance are often encoded in plasmids, which may be transferred by bacteriophages. Consequently, antimicrobial resistance is inevitable, establishes itself and spreads quickly, and is unremitting.

The development and spread of resistance in the community is facilitated by unnecessary prescriptions for antibiotics (more than 40 million unnecessary scripts were issued in 2016 in the USA alone) and the widespread use of antibiotics in agriculture. Within medical institutions, hand-washing, the most cost effective and efficacious method by which to reduce the spread of microbial infections, is frequently neglected. Poor training, lack of knowledge, lack of decision-making and treatment protocols and lack of supervision, regulation, surveillance and accountability exacerbate inappropriate antibiotic prescribing.

Attention to antibiotic stewardship is urgently required and is the responsibility of all health care workers. Simple solutions that can be implemented immediately are listed in Table 8.

<table>
<thead>
<tr>
<th>Table 8. Strategies to reduce emergence and spread of antimicrobial resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Training of all staff</td>
</tr>
<tr>
<td>Implementation and constant review of decision-making algorithms</td>
</tr>
<tr>
<td>Monitoring of antibiotic-prescribing practices and errors</td>
</tr>
<tr>
<td>Hand-washing visible and available (signage and reminders; constant training of personnel)</td>
</tr>
<tr>
<td>Cubiced rooms</td>
</tr>
<tr>
<td>Multidisciplinary team to supervise infection management, with clinical pharmacist and microbiologist in supervising roles</td>
</tr>
<tr>
<td>Infection control protocols, with constant surveillance</td>
</tr>
</tbody>
</table>

References

illness position statement from the European Psychiatric Association (EPA), supported by the European Association for the Study of Diabetes (EASD) and the European Society of Cardiology (ESC). European Psychiatry 2009; 24: 412-424.


