Psychedelic drugs – psychology of pain – the gut and the brain – the impaired physician – views from the Cipla Psychiatry Forum 2017

**KEY MESSAGES**

- Evidence for the use of psychedelic drugs in major depressive disorder is encouraging in carefully selected patients.
- Low-dose ketamine is useful in treating patients with resistant major depression without psychoses.
- Pre-emptive analgesia and management of preoperative anxiety can improve postoperative outcome.
- Interaction with horses with supportive psychotherapy improves participants’ insight into and ability to deal with emotions, interpersonal relationships and behaviour.
- Normal gut microbiota is disturbed by emotional stress and clinicians should consider this aspect in their lifestyle advice to patients.
- Assessment of an impaired colleague should focus on achieving appropriate treatment and compassionate assistance to recovery.
- Testing for at-risk genes in psychiatric medicine demands.

**Getting high to get happy: Are psychedelic drugs the next revolution in the treatment of depression?**

Major depressive disorder (MDD) is the leading cause of disability worldwide. It has a significant impact on quality of life for both affected individuals and their families, on society in general and on the economy in terms of loss of productivity and healthcare costs. Management can be difficult and, despite the wide range of pharmacological therapies available for MDD, response to pharmacological treatment is disappointing. Approximately one-third of patients remit with initial treatment and only two-thirds remit with polypharmacy. This leaves at least one-third of patients who do not recover.

Psychedelic drugs have been used for celebratory, recreational, religious or medicinal purposes for millennia, and their possible role in the management of MDD has been a topic of interest for over 60 years. In the 1950s, psychedelics were used to facilitate the management of MDD with psychotherapy, and in the 1960s, in combination with counselling, lysergic acid diethylamide (LSD) was shown to reduce anxiety, depression, pain and the need for analgesia in patients with advanced cancer. However, practical issues and the introduction in the USA of the Controlled Substances Act in the 1970s ended studies in that country, limiting research to a few studies of LSD-assisted psychotherapy in Europe. Recently there has been renewed interest in the potential role of psychedelic drugs to support psychotherapy in patients with...
MDD and other psychiatric disorders.

Ketamine is a N-methyl-D-aspartate (NMDA) receptor antagonist whose antidepressant effects were first reported almost 20 years ago. Nevertheless, until recently there has been little research on its utility in MDD. The precise mechanisms of the antidepressant effects of ketamine are not fully understood. It is unlikely that NMDA antagonism alone is responsible, since the mood-altering effects of ketamine outlast its bioavailability (suggesting that there may be ongoing downstream effects beyond NMDA antagonism) and other NMDA antagonists do not have comparable antidepressive actions. Recent studies have suggested that antidepressant effects are probably attributable to activation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, leading to upregulation of mammalian target of rapamycin (mTOR) and expression of brain-derived neurotrophic factor (BDNF).

Renewed interest in ketamine for treatment of severe MDD has prompted further investigations and new phase III studies aiming at the registration of ketamine for MDD are expected to commence in 2018. Currently, however, it is not clear which patients may benefit most from treatment. The strongest evidence supports the use of ketamine for a treatment-resistant major depressive episode (MDE) without psychosis, but data are limited to up to one week post infusion. It is uncertain how long the benefits are sustained and the safety of repeated administration over months or years is unknown. Risks and benefits in terms of depression severity, duration, previous treatment and treatment urgency need to be carefully considered. The typical doses that are of benefit are lower than those used for anaesthesia (0.5mg/kg IVI in saline over 40 minutes) and, although this dose is generally well tolerated, there remains a risk of life-threatening cardiovascular adverse effects and sudden mental and behavioural changes. Clinicians using ketamine need to be appropriately trained and prepared to manage such occurrences.

‘Classic’ psychedelic substances may be divided into two groups, based on their mechanism of action.

1. 5-hydroxytryptamine (5-HT) 2A receptor agonists, e.g. LSD, psilocybin (magic mushrooms), dimethyltryptamine (DMT) and mescaline.

2. Serotonin-releasing agent, methylenedioxymethamphetamine (MDMA).

Despite the widespread community use of these drugs, with millions of doses having been consumed over the past few decades, well-documented case reports of long-term mental health problems associated with them are rare. Furthermore, controlled studies have also not indicated long-term mental health problems associated with their use. In a large observational American study including more than 21 000 individuals reporting lifetime psychedelic use, there were no significant associations between lifetime use of any psychedelics, lifetime use of specific psychedelics (LSD, psilocybin, mescaline, peyote), or past-year use of LSD and an increased rate of any of the mental health outcomes. On the contrary, in a number of cases, psychedelic use was associated with a lower rate of mental health problems.

Accordingly, a number of studies are ongoing to investigate the utility of these psychedelic substances in combination with psychotherapy in various mental disorders, including depression, anxiety, post-traumatic stress disorder and recovery from addiction to alcohol, cocaine and tobacco. To date, encouraging results have emerged, including for psilocybin in the management of treatment-resistant depression. However, these results need to be interpreted with caution. Studies are mostly small and, because it is difficult to design clinical trials for these drugs that are double blind and placebo controlled, most are open-label and non-comparative. Better designed, large studies are required to confirm efficacy and safety and to guide therapeutic use before treatment with these agents may become a recognised option for the treatment of patients in everyday psychiatric practice.
Mechanisms worsening chronic pain, including psychological factors

Dr Fanie Meyer

Chronic pain is strongly associated with psychiatric comorbidities, in particular 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 the severity of anxiety, depression or sleep problems, and those with multiple predisposing factors are at highest risk.

Both the peripheral and central nervous system (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 hypothalamic-pituitary-adrenal axis (HPA) is under direct control of various brain pathways, including the hippocampus and amygdala, 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. Furthermore, these changes also lead to activation of immune cells, with a resultant increase in the 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 corticotrophin-releasing hormone, which further increases glucocorticoid activity, increased glutamate release and excitotoxicity, with resultant neuronal cell death and demyelination, and a reduction in modulating growth factors, such as BDNF.

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).

Prolonged or inappropriately managed acute nociceptive pain may result in sensitisation of the peripheral (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, leading to loss of inhibitory control in the spinal cord (disinhibition).

Therefore, given 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 1) along with 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.

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).

Table 1. Multidisciplinary management of chronic pain

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

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

Adapted from references 8-14. Image from: https://www.slideshare.net/ragsamkhamoh/diabetic-p-neuropathy

TCA: Tricyclic antidepressant; NSAID: Nonsteroidal anti-inflammatory drug; SNRIs: Serotonin noradrenaline re-uptake inhibitor (venlafaxine, duloxetine); α2δ-ligand (pregabalin, gabapentin)
Equine-assisted psychotherapy

Dr Helena Lategan

Equine-assisted psychotherapy is an experiential treatment during which individuals interact with horses in a variety of activities, including grooming, walking, feeding and games to gain better personal insight and improve psychological health. Horses are social animals, responding to a natural hierarchical structure, and have an acute perception of mood and emotions. Accordingly they respond to clients’ body language and assertiveness, and mirror it back, providing instant and accurately congruent feedback on their emotional state.

Equine-assisted psychotherapy is conducted by a team of appropriately trained specialists, including a therapist who takes care of the client emotionally and a horse specialist who interprets and translates the horse’s behaviour, ensuring the safety of both client and horse. Therapy focuses on four components: the client’s experience, the horse’s experience, what the experience means to the client in terms of their psychological state and how that experience may be carried forward into everyday life. With the assistance of the therapist, by reflecting on their experiences, thoughts, behaviours and patterns of interaction with the horse, clients gain insight into their current emotional state and approach to interpersonal relationships.

Benefits of equine-assisted psychotherapy include the following:\(^{15}\)

- Assists in becoming aware of interpersonal styles and the impact of those on others;
- Assists in developing insight and new skills to transfer to daily life;
- Assists in becoming more in touch with feelings, thoughts and reactions and in learning to express emotions more congruently;
- Encourages risk-taking and taking responsibility, and developing coping skills for day-to-day life;
- Aids in decision-making;
- Provides an opportunity for growth and learning in a non-threatening and motivating environment.
- Assists in the empowerment of people and builds confidence.
- Teaches empathy, patience and a more effective ability to observe and interpret the behaviour of others;
- Aids in breaking down defence barriers or ‘masks’;
- Enhances relationship-building, effective communication skills and self-esteem; promotes empowerment and change from dysfunctional ineffective behavioural patterns to more successful alternatives.

Applications include management of behavioural and emotional issues, including attention deficit disorder, substance abuse, eating disorders, depression and anxiety, relationship problems and communication difficulties.

More information about practice of and training in equine-assisted psychotherapy may be obtained from the Equine Assisted Psychotherapy Institute of South Africa (EAPISA), http://www.eapisa.co.za.

The gut microbiome: Its role in health and disease

Dr Dominic Giampaolo

The microbiota of the human body is a diverse ecological community of commensal, symbiotic and pathogenic microorganisms, weighing around 2.2 kg. The microbe to human cell ratio is approximately 10:1 and gene ratio 100:1. In healthy people, the range of organisms is diverse, both between individuals and in the same individual, and variable depending on body location, such as vagina, gut and skin. The reason for such diversity is not fully understood, but diet, environment, host genetics and early microbial exposure play a role. In contrast, many disease states are characterised by lack of microbial diversity.\(^{16-18}\) Microbial species
are common to and shared among individuals within families and social communities, where they may be protective against pathogenic organisms and also influence social behaviour.

The gastrointestinal microbiota is the largest reservoir of human flora, representing a mixed population of approximately $10^{14}$ organisms, of which about 95% are bacteria. It comprises approximately 300-500 bacterial species, comprising nearly two million genes (the microbiome). It is established during the first three years of life and is primarily derived from maternal vaginal and faecal micro-organisms obtained during vaginal delivery, evolving during breastfeeding and transition to solid foods. In contrast, caesarean section is associated with delayed establishment, reduced diversity and altered bacterial composition of the microbiome during infancy and childhood, as is excessive cleanliness and early use of broad-spectrum antibiotics.

The gut microbiota plays an essential role in many aspects of health. These include colonic fermentation of dietary fibre; extraction of nutrients; vitamin synthesis; prevention of colonisation by pathogenic organisms; maturation of the intestinal epithelium; maturation and modulation of local and systemic immune responses; release of metabolites to the systemic circulation; and modulation of gastrointestinal hormone release, neurotransmitters and nerve function.20

There are multiple direct and indirect pathways that maintain intensive and extensive bidirectional interactions between gut microbiota and the CNS (cerebral cortex, limbic system and brainstem) involving endocrine, immune and neural pathways. This brain-gut axis maintains normal immune function, stress response and control of inflammation, and gut function. Emotional stress may have profound effects on gastrointestinal function, including alterations in gastrointestinal motility, visceral perception, gastrointestinal secretion, intestinal permeability, regenerative capacity of gastrointestinal mucosa, mucosal blood flow and intestinal microbiota.21

Considering the importance of the gut microbiome in physiological development and homeostasis, and its close association and interaction with the brain and immune system, it is not surprising that disruption and alterations of the normal flora (e.g. by broad-spectrum antibiotics, excessive cleanliness and use of antiseptics, dietary changes) may also influence health outcomes (Table 2).22-26

In contrast, restoration of the gut microbiota may have a significant role to play in prevention and treatment of these conditions. Therapeutic approaches that might be helpful and for which clinical studies are ongoing include dietary changes (including intermittent fasting) and supplementation with pro- and prebiotics (e.g. yoghurt, kombucha [tea], kefir [fermented milk], kimchi [fermented vegetables], pickles). Faecal transplant is a potential therapy that may have utility in many diseases, including anorexia nervosa, autoimmune disease, infections (especially Clostridium difficile), inflammatory bowel disease, obesity and multiple sclerosis.25

<table>
<thead>
<tr>
<th>Table 2. Possible clinical consequences of alterations in gut microbiota19, 22-26</th>
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<tbody>
<tr>
<td>• Inflammatory and irritable bowel syndromes</td>
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<td>• Asthma</td>
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<td>• Obesity</td>
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<td>• Insulin resistance and diabetes mellitus</td>
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<td>• Cognitive changes during aging</td>
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<td>• Non-alcoholic fatty liver disease</td>
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The impaired physician, the HPCSA and the psychiatrist

Dr Shaquir Salduker

Medical practitioners are at high risk of mental illness, including depression and substance abuse. The potential consequences of practising under these circumstances are far-reaching and potentially devastating, occasionally placing the lives of both doctors and patients at risk. Consequently, it is essential that impaired practitioners be assisted to manage their condition safely, which might necessitate temporary or, less commonly, permanent discontinuation of practice.

An impaired doctor is defined as one who is unable to practise medicine with reasonable skill and safety, because of physical or mental illness, including substance use disorder. In 1996, the HPCSA established a multidisciplinary health committee (currently consisting of two psychiatrists and additional members with a special interest) to set out guidelines for reporting, assessing and managing impairment among health professionals registered with the council. Disciplinary matters, if they arise, are managed by a separate committee.

The role of the health committee is to receive reports of impairment, to determine whether the complaint is valid, liaise with the relevant practitioner, arrange for assessment of the allegedly impaired practitioner, discuss and reach conclusions on action and to monitor progress. It must be emphasised that the primary aim of this committee is to protect the safety of patients, and the approach to the impaired practitioner is nonpunitive. Accordingly, self-reporting is encouraged and is considered a mitigating factor by the committee when making recommendations on further action. Under such circumstances, when the practitioner is compliant and willing to accept help, the initial hearing is kept informal. Possible outcomes of the assessment process are listed in Table 3.

Table 3. Possible outcomes of assessment of an impaired practitioner

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<table>
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<tbody>
<tr>
<td>1</td>
<td>Not impaired, not ill: No action. A practitioner may currently be well, but at risk of becoming ill and unable to practise (e.g. bipolar mood disorder).</td>
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<td>2</td>
<td>Ill and not impaired: A practitioner may fulfil criteria for a medical illness or substance use disorder, but still be fit for practice. Treatment may be required.</td>
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<tr>
<td>3</td>
<td>Ill and impaired: Requires supervision and/or treatment; may require restrictions of practice, prescription authority or location of practice; may be permanently ill and unable to practise.</td>
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<tr>
<td>4</td>
<td>Suspension pending treatment outcomes.</td>
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<tr>
<td>5</td>
<td>Being struck off the register.</td>
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Assessment of an allegedly impaired practitioner

A practitioner who requires assessment for impairment might be an existing patient who is receiving treatment, or one who has been referred for assessment by the health committee. Especially in the case of practitioners who fall into the former group, many doctors are reluctant to report a potentially impaired colleague (Table 4) and may be uncertain whether that individual’s illness renders them impaired. However, it is helpful to remember that there is a legal and moral duty to report impairment and that the aim of the committee is not to punish the practitioner, but rather to assess whether they are actually impaired and, if they are, to assist them to obtain appropriate treatment. Consent is not required to report an impaired colleague who is a patient, but it is preferable to encourage them to approach the committee for assistance voluntarily (self-reporting).
Table 4. Reasons for reluctance to report an impaired colleague

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<thead>
<tr>
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<th>Reason</th>
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<tbody>
<tr>
<td>1.</td>
<td>Fear of repercussions.</td>
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<td>2.</td>
<td>Loyalty (conspiracy of silence).</td>
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<td>3.</td>
<td>Misplaced empathy and compassion. Feeling that ‘it could be me’; that the impaired colleague might be at risk of losing their career if they are reported.</td>
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<td>4.</td>
<td>Concern that reporting might be interpreted as professional jealousy.</td>
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<td>5.</td>
<td>Business or financial conflicts of interest.</td>
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<td>6.</td>
<td>Apathy and feelings of not being responsible for the behaviour of others.</td>
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<td>7.</td>
<td>Longstanding therapeutic relationship.</td>
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<td>9.</td>
<td>Choosing to take personal responsibility for the colleague and their illness.</td>
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When assessing a colleague for impairment, the consultation should be kept formal. The patient may be anxious and should be put at ease. The assessment process and possible outcomes should be clearly explained, with reassurance that the process is non-punitive and intended to provide compassionate assistance. It is essential for the assessment to be a comprehensive one. It requires a full medical history and examination, and complete assessment of mental state supported by collateral information from family (spouse) and/or colleagues. Consent should be obtained before seeking collateral information. Necessary investigations may include blood tests, supervised urine screens, appropriate radiological investigations and an EEG. Psychometric tests (e.g. personality inventory, projective tests, neurocognitive assessments) may also be required. During the examination, the examining practitioner is not obliged to divulge reasons for specific assessments or the findings thereof.

A detailed report is then provided to the HPCSA health committee, listing all findings and test results, a diagnosis, an opinion as to prognosis, and recommendations for treatment and further referral. A recommendation as to whether the practitioner is considered to be impaired or not and their fitness for practice should be stated.

While it is understandable that an impaired colleague can present an uncomfortable dilemma in terms of whether to report them or not, it must be borne in mind that the HPCSA committee has been formed to ensure the safety and well-being of patients and to assist, rather than penalise, the impaired practitioner. Medical practitioners are ethically, morally and professionally bound to assist, report and treat impaired colleagues.
The ethics of testing for causative or at-risk genes

Professor Dana Niehaus

The pathophysiology of most genetically inherited diseases that manifest in later life is complex and multifactorial. Phenotype is influenced by a complex interaction between an array of genes and personal and environmental factors, such as parental age at conception and during pregnancy; and exposures to various agents during life, such as radiation, stress and diet. Consequently, there are as yet few reliable or conclusive tests to detect those at risk. Nevertheless, ‘surveillance medicine’, where genetic testing is offered directly to consumers by for-profit companies, is a growing industry.

While genetic tests are advertised to help individuals plan for the future, take preventative steps where feasible and facilitate early diagnosis through regular and intensive monitoring, there are a number of ethical issues associated with the conversion of a healthy person into a ‘patient in waiting’.

Tests are often nonspecific and frequently aimed at detecting genes that may infer a potential, but not certain, risk of a particular illness or group of different illnesses. This means that interpretation of the test results can be problematic, leaving both patients and doctors uncertain about how and for which illness to prepare.

One example concerns testing for the e4 allele of the apolipoprotein E (ApoE) gene, which is associated with an increased risk for both cardiovascular disease (CVD) and Alzheimer’s disease (AD). In a large observational study of more than 1000 customers who had been tested for the e4 allele to detect risk of AD, there was no difference between those testing negative and those testing positive (e4-heterozygotes and e4-homozygotes) for the gene when it came to their intention to make healthy lifestyle changes (diet and exercise). However, homozygotes were more likely to report changes in use of vitamins or nutritional supplements and an intention to make insurance changes. While cardiovascular risk factors, such as hypertension, hypercholesterolaemia and diabetes are associated with an increased risk of AD and CVD, and living a heart-healthy lifestyle might reduce those risks, both of these changes reported by those testing positive are of doubtful benefit and are likely to incur additional expense. On average, those testing positive also showed elevated levels of distress.

In this context, it is worthwhile noting that at least 20% of AD may not have a genetic aetiology and, even when it does, the ApoE gene accounts for only 20-30% of late-onset AD. Conversely, up to 50% of people with a single ApoE e4 allele never develop AD. Therefore, although the presence of ApoE e4 increases the risk of AD, it is neither sufficient nor necessary for developing the disease.

So how does one advise members of the public who are considering genetic testing to determine a future health risk? Testing should always include informed consent. The following checklist may provide some further guidance:

1. Will the test contribute to diagnosis and/or treatment?
2. How likely is a genetic aetiology?
3. Does the patient have the capacity to consent?
4. Who else in the family should be present (or consulted) for a discussion of possible genetic aetiology and testing?
5. What will be the effect of testing on other family members, and do they want to know?
6. Will medical insurance cover testing, or can the family pay out of pocket?
7. How will testing affect insurance coverage for asymptomatic individuals?
References


15. Equine Assisted Psychotherapy Institute of South Africa.


