

# The overlap of research and clinical practice is finding new ways to successfully treat mental illness

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Linda (not her real name) was living a model life. An executive overseeing 300 staff with a supportive family, the 46-year-old was flying high. Then one day everything changed. Seemingly out of the blue she could not focus, could not concentrate and before long could not even get out of bed.

She had no history of mental illness or [depression](#), and clinicians struggled to find a treatment for Linda. For two years she endured psychotherapy, five different types of antidepressants, shock therapy and three periods of hospitalisation. Nothing worked.

Linda was then referred to Professor Jayashri Kulkarni, head of the Women's Mental Health Clinic at the Monash Alfred Psychiatry research centre (MAPrc), of which she is also director.

Linda underwent novel [hormone treatment](#) for depression using oestrogen – a world-first developed by Professor Kulkarni and her team at MAPrc that draws on the research expertise of Monash University and the clinical setting of Melbourne's Alfred hospital. Within two months she was back to her old self. "She has returned to work ... it's everything you would hope to see," Professor Kulkarni says.

Linda's recovery is just one of the stories coming out of MAPrc, which provides new approaches and solutions to people suffering from mental

illness for whom standard treatments have failed.

"We are seeing some spectacular turnarounds for people who have been virtually moribund with depression," Professor Kulkarni says.

The MAPrc's point of difference is its ability to translate research into clinical practice. "We are in the privileged position of being able to draw on the university resources and the background of basic science, but we are also part of a hospital, and in psychiatry I think that's vital. We can offer new treatments, new services, along with a new understanding of conditions."

This was the case for Linda, who was able to undergo psychiatric treatment while participating in a trial for the new hormone treatment developed at the centre.

The three clinics operating out of MAPrc specialise in women's health, magnetic brain stimulation (known as transcranial magnetic stimulation) and treatment for voice hallucinations. The psychiatrists who run the clinics also oversee research programs in their area of expertise.

In a cyclical fashion, the clinics also help to shape new research directions, Professor Kulkarni says. "The research informs the treatments but then the patients provide the next round of questions."

## **Sobering statistics**

For many, MAPrc's unique services are a last resort. Referrals come from across Australia and around the world for patients who have not responded to conventional treatments.

Statistics show that in Australia one million people – almost one in 20 – suffer from a mental illness that does not respond to traditional

treatments such as antidepressants or, for the very unwell, electroconvulsive therapy, commonly known as shock treatment.

Globally, the World Health Organization says more than 450 million people (about 6.5 per cent of the population) suffer from brain disorders but that many more have mental problems, which are experienced as psychological disturbances.

In the US, the UK and Australia, the diagnosis figures are higher than the global average. Health authorities in the US and UK report that one in four adults will experience a mental health problem in the course of any given year.

In Australia that figure is one in five, and Professor Kulkarni says women are more likely to be affected than men, with one in four suffering from depression or anxiety at some point in their lives.

Women are often the linchpin in families, caring for elderly parents, children and often working in paid employment, Professor Kulkarni says. If depression in women is left untreated, "there are three different sectors that fall down when she falls down".

## **Women's business**

One of MAPrc's five research streams, Professor Kulkarni's world-leading work into women's mental health has led to several breakthroughs in treating mental illness, particularly the novel use of hormones and especially the potent brain steroid oestrogen.

Professor Kulkarni has discovered that oestrogen is successful in treating women with schizophrenia and, more recently, perimenopausal women suffering from depression.

This includes women such as Linda, who previously functioned without any sign of depression. Professor Kulkarni also developed a rating scale, the Meno D, to detect depression in menopause. "There is a 16-fold increase in depression in middle-aged women – and it is not just coincidence," she says.

Oestrogen has also been effective for younger women suffering depression either on a cyclical monthly basis or postnatally. At both such times women can develop depression related to hormone shifts in the brain, but they do not necessarily respond well to standard antidepressants.

Studies into the use of oestrogen for depression have now been replicated in the US, China and Spain, and its use is filtering out more broadly into the community as referring physicians see its effect and begin prescribing it themselves.

Professor Kulkarni has now also turned some of her research focus to the changed hormone levels in young women suffering mental illness as a result of sexual or physical abuse – a group increasing in prevalence in official statistics and at her clinic.

These patients exhibit features of chronic post-traumatic stress disorder and an increase in the stress hormone cortisol, linked to obesity, fertility problems, trouble concentrating and changed brain circuitry.

Treatment for such women should be multifaceted, she says, incorporating hormone treatment and therapies with services such as legal advice and social work. At MAPrc, which takes a multidisciplinary approach, such a comprehensive strategy is possible.

## **Multidisciplinary buzz**

The MAPrc was established by Professor Kulkarni, Professor Paul Fitzgerald and Anthony de Castella in 1994, when all three were young researchers at a suburban hospital in outer Melbourne, and 20 years later all three are still together at the helm. The centre has operated in partnership with The Alfred, a major metropolitan hospital, since 2002, when Professor Kulkarni was appointed its chair of psychiatry.

The team aspires to operate like the Mayo Clinic in the US, the world's first and largest integrated not-for-profit medical group practice, which also houses multiple research streams and a diverse group of staff.

At MAPrc, researchers and clinicians from different fields often collaborate on the centre's 100-plus projects. Staff specialities include medicine, psychiatry, pharmacology, physics, endocrinology, engineering, fundamental science and even art. Researchers are also appointees of Monash or Swinburne University of Technology, and dozens of undergraduate and postgraduate students from both institutions consistently rotate through the centre.

Recently, a statewide assistance program for problem gamblers was established at The Alfred thanks to a MAPrc project, which found that up to 80 per cent of problem gamblers experience suicidal thoughts and 23 per cent had attempted suicide. The research was triggered after nurses told MAPrc staff that many suicide-attempt patients had mentioned gambling problems. Professor Kulkarni describes the project, financed by the Victorian Department of Justice, as "action research".

"The centre is full of people who are incredibly enthusiastic and we all share that passion. But what really keeps us going is when you have someone like Linda. She improved. She waltzed out of here and that just made our day, our week, our month."

## **Psychiatry's tilt at better diagnoses**

Measuring a brain's electrical activity while someone sits comfortably in a special tilt chair is the future of [mental illness](#) diagnosis, says Monash Alfred Psychiatry research centre (MAPrc) director Professor Jayashri Kulkarni.

The innovation – EVestG – won the Australian Broadcasting Corporation's New Inventors television series in 2010. It is regarded as a major advance in [mental health](#), quickly and accurately measuring a biological marker for psychiatric conditions.

EVestG researchers have recently focused on diagnosing the difference between bipolar affective disorder and depression. Diagnosis of bipolar and depression is problematic, says Dr Roger Edwards, CEO of Neural Diagnostics, MAPrc's commercial partner for the technology. This is because people with bipolar disorder who seek treatment are often experiencing the depression phase at the time. This often results in the misdiagnosis of bipolar disorder as depression, sometimes repeatedly. And in a person with bipolar disorder, antidepressant medications can cause an episode of mania.

The EVestG (electrovestibulography) diagnosis is based on signals emitted from the brain as the patient's balance – or vestibular – system is challenged by the chair tilting them into different positions.

## **Balancing act**

A probe in the patient's ear canal measures signals from the brain's balance organ. These are processed by a computer, which prints a readout of electronic impulses similar to an electrocardiogram (ECG).

The key to the system is a discovery by EVestG's inventor, MAPrc Adjunct Professor Brian Lithgow. Several years ago while researching

balance-related disorders, he noticed consistent anomalies in brain readouts – or vestibular-evoked responses – of people with Parkinson's disease and depression. When deliberately moved off-balance, the vestibular-evoked response readout of someone with a mental disorder such as bipolar was different to that of a healthy person.

People's responses (shown in the ECG-like readout) as they are tilted will be similar according to their particular disorder. For example, those with [bipolar disorder](#) will produce a reproducible, similar pattern. Likewise, people with depression will produce a different reproducible pattern, as will people who are healthy. Professor Kulkarni, EVestG co-developer and principal clinical investigator, says the technology works because the vestibular (balance) system is closely linked to the brain's limbic (emotional) system. They develop at about the same time in a foetus and are closely associated in terms of neurochemistry and neurocircuitry.

"We are using the balance system as a window to the emotional brain," she says "And this window could allow researchers to diagnose a condition objectively when it is compared to a large, normative dataset."

Dr Edwards says the diagnostic accuracy in trials of people with depression and schizophrenia has been more than 85 per cent. This is a 20 to 50 per cent improvement on current diagnostic methods, which are subjective.

With the University of Manitoba in Canada, where Adjunct Professor Lithgow is now based, researchers are building a bigger dataset so that EVestG technology can be used in clinical practice.

## **Magnetic power**

Professor Paul Fitzgerald, deputy director of the Monash Alfred

Psychiatry research centre (MAPrc), uses advanced neuroscience to investigate brain function. Among his team's achievements is a contribution to a world-leading non-drug treatment for depression that is being adopted around the world as standard clinical practice.

People who have suffered from depression for as long as 30 years are now improving after a four to six-week course of daily treatment with [transcranial magnetic stimulation](#) (TMS). After each session, which lasts less than an hour, they can walk out and drive home.

"Our response rates are typically somewhere between 30 and 50 per cent, depending on the patient, but they all have severe treatment-resistant depression and have had multiple courses of other treatments, including multiple medications, psychotherapies and sometimes electroconvulsive therapy, and not got better," says Professor Fitzgerald, who heads the MAPrc psychiatric neurotechnology stream.

"Our expectation is that their depression will be resolved – meaning a person is able to return to work or study or their typical daily activities."

TMS works by realigning the brain's biochemistry through stimulation of neural pathways. Unlike antidepressants, it has few, if any, side effects.

"There is a theoretical risk of causing a fit but we have never had a single seizure in more than 10 years of treating patients," Professor Fitzgerald says.

Because no drugs are involved, TMS is suitable for people who have either not responded to antidepressants or who may suffer unacceptable side effects from them. Patients are awake during the treatment, in which a hand-held, plastic-coated coil is placed close to the scalp, creating a magnetic field that stimulates electrical activity in the brain's nerve tissue. Particular areas of the brain that are either underactive or overactive are targeted, depending on the illness.



Over time, TMS can increase or decrease activity in certain brain regions, potentially reconnecting the circuitry between areas of the brain relevant to depression.

Professor Fitzgerald was among the international pioneers of TMS, which in the mid-1990s was used by researchers to measure brain activity.

Today, his TMS clinic runs alongside a complementary research unit that in turn helps to advance treatments. Research is underway into potential use of TMS to assist people suffering from schizophrenia and autism.

"We have also started to branch into other brain stimulation methodologies beyond TMS, including magnetic seizure therapy and deep [brain](#) stimulation," Professor Fitzgerald says.

Provided by Monash University

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