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Featured article **Neurobiology of depression – examining resilience to stress**

Why are some people more resilient to stress than others and is there a neurobiological basis to resilience that could help inform management of depression? During an APA symposium “Deconstructing the neurobiology of depression” several speakers described the latest concepts. We report.

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Schizophrenia

New insights on schizophrenia caregiver burden: impact on work and productivity

Hot on the heels of a study showing that at least 8.4 million Americans provide care to an adult with an emotional or mental health issue, comes further information highlighting caregiver burden. We report from an APA Scientific and Clinical Reports session which featured findings of a survey of schizophrenia caregivers.



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Imagine if one working week every month your work performance was limited or compromised. That's the situation faced by many schizophrenia caregivers who also hold down paid jobs, according to the findings of a large-scale caregiver survey presented by Dr Debra Lerner of the Tufts Medical Center, Boston, at the 2016 APA congress.

Dr Lerner said that over 18% of adults in the US act as unpaid caregivers, and she cited the findings from On Pins and Needles study which showed that three quarters of caregivers looking after someone with mental health issues find the task emotionally stressful.

Holding down a job

Many caregivers to people with schizophrenia and schizoaffective disorder work, and Dr Lerner therefore said it was important to try to understand the impact that their caregiving had on work function and productivity. To this end, Dr Lerner got involved in conducting a survey of caregivers who also worked, asking about their paid work commitments and employment.

She described the anonymous on-line survey, which included a number of validated tools such as the work limitations questionnaire (WLQ), designed to assess time lost from work (absenteeism), presenteeism and impact of caregiving on work productivity.

Results from over 1000 caregiver questionnaires were available for analysis, and showed that the average age of caregivers was 55 years, with the average age of the care-recipient 40 years. Most caregivers were women and most were the parent of the person with schizophrenia or schizoaffective disorder.

Heavy work commitments

Over 60% of caregiver respondents were in current work and of those, 69% reported being in full time

work. Dr Lerner said that these statistics showing high rates of full time work among carers, emphasized the need to make things easier for caregivers, particularly as the survey showed that most worked outside of the home and many had lengthy commutes to their place of work.

Work losses common

Over a quarter of caregivers in work said they often had to take time off work but more than half said it was difficult to take time away from work for personal matters. Missing an average of 0.6 days per week from work and associated with work productivity losses of around 8%, Dr Lerner said that caregivers had work losses that are equivalent to those experienced by patients with MDD.

The survey highlights that being a caregiver to a person with schizophrenia spills over into work – with a negative impact on productivity. More research is needed to understand and quantify the burdens on those who care for people with serious mental illness.

Dual disorders – confusion and neglect



Dual disorders – sometimes referred to as dual diagnosis – is a term applied to describe the co-occurrence of substance-use plus mental illness. But there has been lots of confusion and inconsistency in terminology that has hampered consistent reporting of this common state of affairs. At an APA symposium on dual disorders, experts tried to bring some clarity to this poorly understood and often overlooked psychiatric diagnosis.



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Too many acronyms for dual disorders mean that it is hard to interrogate the literature and understand the true prevalence of co-occurrent substance abuse and mental illness. So said Dr Shaul Lev-Ran of the Addiction Medicine Service at the Sheba Medical Center and Tel Aviv University, Israel, during an APA symposium on dual disorders.

Two for one

Dr Lev-Ran said confusion and lack of consistency in naming ‘dual disorders’ continues to plague good documentation of how often mental illness and substance abuse collide. Adding to the difficulty in defining and describing the rate of this co-occurrence of mental illness and substance abuse is the fact that one condition may beget the other, and the additional fact that in people with mental illness, there is a lifetime risk of increased substance use – which is not quite the same as concurrent substance use.

Between the cracks

Of concern, is that people with co-occurrent mental illness and substance use disorder may “fall between the cracks” when it comes to receiving optimal care, Dr Lev-Ran said.

More common than thought

Dr Lev-Ran referred to a number of reviews in recent years which have attempted to assess data from clinical samples and comorbidity studies, and reach a value for the prevalence of dual disorders. The most recent reviews looking at patients with psychiatric diagnoses, who are receiving treatment, suggest that around 50% of patients with schizophrenia may have substance use disorder, with values less amongst patients with mood disorders.

Drugs and alcohol

Current estimates suggest that among people with substance use disorder, the lifetime prevalence odds ratio for anxiety is 2.5 and for mood disorders is 4.5. However, Dr Lev-Ran said that risks for co-occurrence in a 12-month period are more informative for helping clinicians estimate whether any given patient in their care may be at risk of dual disorder. For example, 12-month estimates are that in drug use disorder patients who are seeking treatment for their substance use, 60% have comorbid mood disorders.

Coming at it from the other direction, among people with mental health issues, it is estimated that in any 12 month period, around 10% of people with MDD may be using drugs and around 20% using alcohol.

Plagued by stigma

Dr Lev-Ran said that there continues to be stigma around substance-use – another factor that potentially under-estimates the true prevalence of dual disorders. Patients may be reluctant to divulge substance use to clinicians, fearing retribution.

Turning to substance-induced mental illness, Dr Lev-Ran and other speakers in the symposium noted that it is important to distinguish between the psychotic and withdrawal effects of substances and true primary diagnosis of a co-occurrent mental disorder.

Dr Nestor Szerman of the University of Madrid, Spain, reminded the audience that nicotine dependence and gambling addiction, now a DSM 5 recognized disorder, are also commonplace in patients with mental health issues.

More to it than reward

During the symposium several speakers touched on the neurobiology of dual disorders, urging the audience to think beyond the simple concepts of activation of dopaminergic reward centres to explain addictive behaviours. Dr Szerman was keen to stress that opioid, endocannabinoid, nicotinic and glutaminergic pathways and activity play a part, as do genetics and lifetime experiences, and in his view, addiction is not simply a disorder of the brain’s reward system.

Dr Lev-Ran called for better definitions and more research into dual disorders in order to bring this psychiatric diagnosis to wider recognition.

Schizophrenia

Cognition in older people with schizophrenia, and retroviruses in the young



Give elders their due

People with schizophrenia aged 55 years and above are about to become 25% of the total population with the disease. Yet only 1% of the schizophrenia research budget relates to older adults. So it is not surprising that much about the natural history of schizophrenia in this group remains unclear. To what extent is it really a quiescent disease at this stage in life? How does cognitive function change with time?

Data from New York City, presented by Carl Cohen (SUNY Downstate Medical Center, Brooklyn, New York, USA) casts light on what is happening in people with schizophrenia in mid to late life (55 years plus) and living in the community.

The starting point was a group of 250 who had developed schizophrenia before the age of 45. They were outpatients and did not have moderate or severe cognitive deficits or complicating factors such as a history of head trauma at baseline. Those living independently represented 39% of the sample: the others were in some form of supported residence. They were matched at baseline with 113 controls matched for age and income.

No mean change does not mean no change

At the start of the study, people with schizophrenia had a mean Dementia Rating Scale (DRS) score of 128, not far below the score of 138 among controls, but perhaps indicative of mild cognitive impairment. As expected, there was considerable loss to follow-up, not least because of death. But those lost were similar to those who could be re-contacted. After a median follow-up of 4.5 years, the mean score of 127 among 104 people with schizophrenia showed no change. But this did not mean that no px had changed. While 59% showed essentially the same score at follow-up, 21% had experienced a decline in cognition – defined as a fall of 0.5 SD per year – and 19% had shown improvement -- defined as an increase in score of 0.5 SD per year. So the cognition the situation is actually quite dynamic.

On multivariate analysis, those whose cognition scores improved had had poorer scores at baseline. So there may be some regression to the mean. Though pxs living independently had better cognition at baseline, those living in supported housing were less likely to show decline over the period of follow-up, perhaps because of greater access to services.

Does pro-schizophrenia RNA hide deep in the genome?

Although an estimated 8% of the human genome is of retroviral origin, acquired during millions of years of primate evolution, most of it is now junk. It has been inactivated by mutation or epigenetic processes such as methylation. But what if some of it is capable of re-activation, perhaps by infections during embryonic development?

Though he repeatedly acknowledged that the idea is highly speculative, Awais Aftab (Case Western Reserve University, Cleveland, Ohio, USA) presented the argument that Human Endogenous Retroviruses (HERVs), particularly the HERV-W family, may play a malign role in the causation of schizophrenia.

There is evidence that HERV-W nucleotide sequences are more common in those affected with schizophrenia than in controls. The HERV-W envelope protein seems to activate production of inflammatory cytokines, which might contribute to the inflammation story in schizophrenia. And infections linked to schizophrenia can activate HERV-W elements, perhaps through demethylation of relevant genes.

In combination with genetic predisposition and environmental factors, archaeological remnants of millennia-old viral RNA could set the developing brain on the path towards schizophrenia and so provide a missing link in causation, at least in some patients. It is a suggestion worth considering.



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The cognition situation in older people is dynamic: some improve, others decline

Schizophrenia Psychiatry and internal medicine: bridging the gap



Patients with mental illness are far more vulnerable than others to physical ill-health. They die decades too soon. As a profession, we should own this problem. Psychiatry and internal medicine need to be better integrated.



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There are medical mysteries, but there are also plain facts. One is that patients with major depression are at increased risk of diabetes and cardiovascular disease. Another is that people with schizophrenia are likely to die 20-30 years earlier than people without serious mental illness.

Robert McCarron (UC Davis, Sacramento, California, USA) urged psychiatrists to respond to the challenge that this represents. Pritham Raj, of the Oregon Health and Science University, Portland, USA, is keen to do so.

Of apples and pears

In the era of metabolic syndrome (defined by abdominal obesity; elevated blood sugar, blood pressure and triglycerides; and reduction in HDL-cholesterol), preventing obesity in our patients is proving tough, he said.

A high body mass index (BMI) is associated with many problems, including pain. In terms of cardiovascular risk, waist to hip ratio may be more important. A ratio greater than one (an apple shaped body) carries a higher risk than when the excess weight is predominantly below the waist (pear shape). In part this may be due stress, since raised cortisol encourages accumulation of abdominal fat.

But weight control and reduction is still a major goal in many people with mental health problems.

Food, feet and fingers

As a starting point, Dr Raj suggests we explain the following things:

- For people taking medication for mental health problems, no specific diet is superior to any other
- The ideal plate – of standard size, and without coming back for more – is roughly half fruit or vegetables, a quarter starch, and a quarter protein
- Calorie restriction can reasonably be expected to achieve weight loss of 1lb (0.5 kilo) per week
- If you are not a vegetarian, white meat and fish are better than red meat

Sweet drinks are highly calorific and diet sodas are not a good substitute: it seems that artificial sweeteners create “psychological freedom” to eat other high calorie foods.

In relation to calorie expenditure, people should get on their feet. It is more helpful to talk about “activity” than about “exercise”. Walking is fine. Spending

at least thirty minutes each day in physical activity of moderate intensity is recommended.

Weight and targets for weight loss should be recorded and discussed during subsequent consultations. If there is no mention in the notes, patients may think these issues are not important.

With respect to fingers, people can be encouraged to find something to do with them that does not involve smoking.

We may also be able to help patients by prescribing medications that are less likely to cause weight gain or increase risk of diabetes. So judicious choice of drugs has a role, and metabolic monitoring is warranted with many medications used in psychiatry.

When lifestyle change is not enough

Lifestyle change is likely to achieve the biggest benefits. If this fails, bariatric surgery – especially sleeve gastrectomy – has a role. But there may be issues of drug and nutrient absorption. And there have been cases of psychiatric morbidity associated with such surgery.

Depression

New insights on inflammation and neuroimmune function in depression

Proinflammatory cytokines and their soluble receptors are increased in the plasma of patients with MDD. Understanding neuroimmune changes in depression might help identify potential new therapeutic targets. We report on a presentation at the APA 2016 focussing on peripheral and central immune markers in depression.



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Inflammation in depression continues to be a hot topic and the subject of ongoing research aiming to deconstruct the neurobiology of mood disorders. Several lines of evidence – both clinical and preclinical - identify that there are increases in proinflammatory cytokines such as IL-1beta, IL-6 and TNFalpha in the plasma of patients with depression. Speaking during an APA symposium, Professor Ghanshyam Pandey, Director of Mood Disorders and Suicide Research at the University of Illinois, Chicago, said that current research hopes to understand why and where these inflammatory markers are increased – looking at both peripheral and central activation of the immune system in depressive states.

Markers or mediators?

He reminded the audience that infusion of cytokines to animals or humans induces a “sickness behaviour” very similar to depression, suggesting that these inflammatory mediators may be more than just markers of immune activation in mood disorders but more fundamental to the neurobiology of disease.

Gene expression

Professor Pandey’s recent research has included study of post-mortem brains of patients hospitalized for depression and bipolar disorder and he has also looked at the expression of genes for the cytokines known to be increased in depressive states. He explained that it is important to measure mRNA expression for both cytokines and their respective receptors.

According to Professor Pandey, expression of IL-1beta, IL-6 and members of the TNF superfamily are all increased in depression and in addition to increased production of these cytokines, there is increased expression of the membrane bound receptors that mediate cytokine effects. He reminded the audience that peripheral cytokines cannot readily cross the blood brain barrier, but he said that the proinflammatory cytokines implicated in depression

are abnormally expressed in the brains of patients with depression and in the brains of patients with mood disorders who committed suicide.

Central up-regulation of cytokines and receptors

Part of Professor Pandey’s research has included study of post-mortem brains from young, adolescent suicide victims where he said that protein and mRNA levels of IL-6 and TNFalpha were increased in the pre-frontal cortex. Studies of adult brains of patients with MDD who committed suicide revealed significant decreases in IL-10 – an anti-inflammatory cytokine, and significant increases in lymphotoxin A (LTA) as compared with otherwise normal control brains. Professor Pandey remarked that in contrast to the increased expression of cytokines themselves, the expression of receptors for these cytokines was decreased.

Taking a toll

Another mediator that has been exciting interest among psychiatrists are toll-like receptors (TLRs) – a family of mediators involved in mediating innate immunity. Professor Pandey said that TLR3 and TLR4 are reported to have effects on cognitive performance, while deficiencies in TLR3 have been shown to help spatial cognition. He said that therapies targeting TLRs have been studied in other conditions with immune components such as HIV2 infection and psoriasis, with research also now extending to study in depression.

Schizophrenia

Cormorbid and complex: achieving good outcome with the “difficult” patient

Motivational interviewing encourages the difficult patient to “talk themselves” into change. It is a technique useful, for example, in comorbid mental health and substance use problems. The session on helping people with complex needs heard equally inspirational talks on cognitive behavioural therapy accompanied – in the case of PTSD – by controlled exposure to sources of stress.



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As a therapist, be fascinated not frustrated; curious not furious.

Person-centred counselling with an emphasis on expressing empathy are key elements in motivational interviewing, as pioneered by Miller and Rollnick. But what makes the technique unique is a systematic strategy designed to create conditions for change by eliciting motives that lie within the individual concerned. The aim is that patients talk themselves into changing. This is the essence of motivational interviewing, described by Steve Martino, Yale University School of Medicine (New Haven, Connecticut, USA).

Shared expertise

There is shared work to be done, and both parties have expertise. Partnership, along with compassion, acceptance and evocation, make up the “motivational interviewing spirit”. We have to believe that there is something that will motivate change, even in a difficult patient who does not seem set on this course. The job of the therapist – along with the patient – is to discover what it is and then plan how the change is to come about. But there is no planning for change without prior commitment.

The therapist is listening for the patient to come out with “change talk”. Ideally, this will be expressed in terms of Desire (I want to), Ability (I can), Reason (it’s important) and Need (I should). Together, they are summarised in the acronym DARN.

Even if the patient seems stuck in talking about all the reasons they should not change (“sustain talk”), the likelihood is that there is some ambivalence; and this should be sought out.

It takes two to tangle

When the situation is not ideal, the therapist can inadvertently contribute to maintaining the “difficult” patient. People are often under external pressure to change from family and the legal system. This is experienced as aversive and they push back. We should try not to contribute to this: avoid a confrontational setting in which the therapist is arguing for change and the patient for no change.

High levels of sustain talk and discord in sessions predict poor outcome. Although sustain talk cannot always be avoided, discord can – since it takes two to tangle. As a therapist, be fascinated not frustrated; curious not furious. Roll with resistance. And recognise that motivation to change will ebb and flow in the course of treatment.

Confronting traumatic memories

Even in cases of severe PTSD, there are highly effective interventions, and it is good to let patients know this, Seth Gillihan, Perelman School of Medicine, University of Pennsylvania (Philadelphia, USA) told the session. →



PTSD is characterised by avoidance: sufferers believe that the world is not a safe place and that no-one can be trusted. Because they avoid going out, they don't encounter corrective information; and they don't talk about the experience.

Part of the antidote is to go into the world and experience the fact that the feared consequences do not occur. Another element is learning that you can recount the trauma memory and not fall apart. In a sense, a frame is put around it.

Frequently, feelings of guilt and lack of competence are part of the disorder. These over-generalisations can also be countered, by drawing attention to information that disconfirms erroneous beliefs.

Perhaps the key element of therapy, though, is for the patient to confront reminders of trauma in a safe environment. There is a process of graded exposure, in imagination and in reality. Gradually, the patient is encouraged to activate thoughts that trigger distress, and to undertake activities that they believe are dangerous – until a sense of mastery is achieved.

Same principles in personality disorder

CBT can also be used effectively in the case of personality disorder, regarded as one of the mental health problems which is most difficult to treat, Judith Beck (University of Pennsylvania, Philadelphia USA) said. The principles are the same as in any other disorder: conceptualize the problem before you try to treat it.

Patients have to accept all three elements in the cognitive model: the idea that the way I think influences what I do; that some of what I think is distorted; and that by changing my thinking I can feel better and behave in a way that brings me closer to my goals.

The target cognitions may differ with different disorders. In the case of depression, for example, they relate to beliefs about the world, the self and the future. In the case of panic, they relate to the catastrophic events that the patient believes are imminent.

But in each case the way people get better is by making small changes every day. Ultimately, the patient has to become his or her own therapist.

Patients talk themselves into changing: we just need to create the right conditions.

Ultimately, the patient has to become his or her own therapist.

Depression

Neurobiology of depression – examining resilience to stress



Why are some people more resilient to stress than others and is there a neurobiological basis to resilience that could help inform management of depression? During an APA symposium “Deconstructing the neurobiology of depression” several speakers described the latest concepts. We report.



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Stress is part of living. Stress shows us to be sophisticated. Our adaptive responses in cognitive and emotional behaviour in the face of stress, are what distinguish humans from animals. Yet some stressors can prove overwhelming, driving stress-induced depression.

Speaking during an APA symposium, Professor Gustavo Tafet of the Maimondes University Department of Psychiatry and Neurobiology in Buenos Aires, Argentina, described the efforts psychiatrists are making to understand why some people are more resilient than others to stress. By characterizing the neurobiological and psychosocial basis of stress-resilience, clues might be found to help in the management of depression.

Adapt and cope

Professor Tafet reminded delegates that whether stress is bio-ecological or psychosocial, the body has two main means of coping: through adaptive responses mediated by neuronal networks, and through neuroendocrine responses mediated by activation of the hypothalamic-pituitary-adrenal (HPA) axis.

Helplessness a gateway to depression

He said that resilience is the ability to continually adapt successfully to stress and to cope with adversity. Without such resilience, too much chronic stress can lead to “learned helplessness” – which he said can be a gateway to depression. In learned helplessness, cognitive resources are decreased, while in resilience, cognitive resources are employed to cope, recover and learn from stress.

In our make-up

Professor Tafet said that early life adversity may play a part in eroding resilience, by generating what he described as a ‘kind of trauma’ in the long-term memory that makes a person more prone or vulnerable to depression in later life. Beliefs and self-knowledge also shape our resilience or susceptibility to stress and more unavoidably – our genes play a part too.

Many polymorphisms have been identified that are linked with increased vulnerability or greater resilience to depression. For example, Professor Tafet said that genetic polymorphisms in the serotonin transporter gene (5HTT) are associated with increased activation of the HPA axis and increases in cortisol - so increasing stress, and he said that polymorphisms in BDNF have been shown to affect neurogenesis and plasticity in ways that affect cognitive processing and

the ability to cope with stress. People with both of these polymorphisms are at increased risk for depression especially if exposed to life stresses.

Professor Tafet said that polymorphisms of the chaperone protein to glucocorticoid receptors render cortisol less effective, leading to a deficient negative feedback on HPA axis activity, and so increasing stress and predisposing towards MDD.

Endogenous sources of resilience

Certain physiological substances may be important for resilience to stress. Professor Tafet said that the naturally occurring glucocorticoid DHEA blocks the effects of cortisol, and neuropeptide Y is another endogenous substance which has been shown to have anxiolytic properties.

Stress and psychosis in depression

Speaking during the same APA symposium, Professor Alan Schatzberg of the Department of Psychiatry at Stanford University Medical School, provided additional insights on the role played by cortisol in stress, and reminded delegates that in the past, attempts had been made to manage certain forms of depression by using cortisol-blocking agents.

Professor Schatzberg said that in patients with depression – increased levels of glucocorticoids – hypercortisolism – may play a role in the development of psychosis, possibly mediated by cortisol induced changes to the regulation of dopaminergic function. He said that although the reported number of MDD patients with depression plus psychosis is quite low, epidemiological studies suggest that as many as 1 in 5 MDD patients have psychotic features.

Once again, genes appear to play a part. Professor Schatzberg said that certain variants for the glucocorticoid receptor contribute to risk for depression and to a degree of psychosis.

Mental flexibility and attitude is everything

Both Professor Tafet and Professor Schatzberg, also described the psychosocial factors and characteristics that are thought to engender stress resilience – features such as optimism, humour, cognitive flexibility, ability to perceive stressful events in less threatening ways and a mixture of altruism and what Professor Tafet described as healthy egotism.

Depression

Interview with Fábio Gomes de Matos e Souza, Professor of Psychiatry

Interview

Fábio Gomes de Matos e Souza, Professor of Psychiatry at the Federal University of Ceará, Brazil



Fábio Gomes de Matos e Souza, Professor of Psychiatry at the Federal University of Ceará, Brazil, discusses the challenges and progress experienced in many years of treating major depressive disorder (MDD).



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We don't want just a reduction in symptoms – we want them to return to good functional roles

Each year, Professor Souza's group sees around a hundred patients with a first episode of depression and cares for a total of 200-250 MDD patients, primarily in an outpatient setting.

What are the most significant challenges facing clinicians treating MDD?

The first is diagnosis. The depression may be unipolar or bipolar, and possibly mixed with other comorbidities such as anxiety and substance use disorder.

The second is education. Patients ask "When will I be cured?" They have to understand that depression may be a chronic disorder. Adherence is fundamental, but the context is that we have agents that are effective, and well tolerated. Families also have to be educated about the need for long-term treatment. And both patients and families need to understand that there may be biological and genetic vulnerabilities.

In severe cases, there may also be risk of suicide. This has to be sensitively approached and managed.

Then come the challenges of treatment.

What is the best approach, and what can be achieved?

We work in a university setting, so we have a team of psychiatrists, psychologists and social workers and can incorporate interdisciplinary working into clinical practice. Medication alone is not enough. Patients may have to modify lifestyle factors such as excessive alcohol and poor patterns of sleep. They need to develop the skills needed to manage conflicts within the family, and to negotiate the workplace: some employers are not understanding when it comes to depression.

So there is also usually cognitive behavioural therapy (CBT). This technique is more research-based than other psychological approaches, and patients tend to respond well and more quickly. They understand the dynamics of it, and you don't have to pull out early

childhood. Given the huge demand, we need treatments that make people feel better as quickly as possible: there is no time for long psychotherapies, even if they work.

What are the most significant advances you have seen?

We now have drugs with fewer adverse effects, less risk of drug interactions, and a lower risk of inducing obesity. We have different drugs that can be suitable for different patients. But the therapeutic challenge is that around 30% of patients don't respond well to the medications usually prescribed. So, despite significant advances in our understanding of depression, there is still a large group whose need for adequate treatment is not met.

What proportion of your patients experience remission, and how do you define it?

For many years, the focus was on response not remission. But a 50% reduction on the MADRS or Hamilton scales is not sufficient. We don't want just a reduction in symptoms – we want patients to be able to return to good functional roles in study and work and emotional life, and to have restored joie de vivre.

So, while perhaps 50% of patients have control of symptoms, maybe only a third achieve remission in this sense.

One reason is that we have not focused sufficiently on cognition. Deficits in memory, attention and executive function can be disabling. Concern with enhancing these areas may improve chances of full remission.

Another is that you lose neurones with each depressive episode. And to achieve remission you need an intact brain. So every effort should be made to avoid the next episode. This means treating not just the episode but the disease. If depression is treated properly, the chances of a next episode can be reduced.