The American Psychiatric Association's 168th Annual Meeting was held in vibrant Toronto, Canada. The theme for this year's meeting — "Integrating Body and Mind, Heart and Soul" — truly captures the spirit and the intimacy of psychiatry. The theme not only captures the relationship between mental health and physical health, but also the interconnections between psychiatry and general medical practice. Our reporters have been busy capturing highlights from in and around the congress. Please enjoy!
Depression

Balancing psychotropic side effects and benefits

»Never take a pill that has more side effects than you have symptoms.«

The caption of this initial cartoon set the scene and amused the audience but did not reflect the tone of the session.

In contrast to the claims of antispsychiatry activists that the harms of drug treatment often outweigh the benefits, what we do overall is clearly helpful to patients, Roger McIntyre (University of Toronto, Canada) told the meeting. That said, an essential part of our duty of care is to minimise the unwanted and unintended effects of treatment.

We all encounter side-effects in our patients, yet we seldom confront them head on, said Joseph Goldberg (Mount Sinai Hospital, New York, USA). Sexual dysfunction, for example, is probably more common than we generally acknowledge. Having a more pro-active approach to the management of adverse events (AEs) would help optimise outcome.

Several other core concepts were discussed
• Side effects and the fear of side-effects undoubtedly contribute to non-adherence, but these factors are not necessarily the most significant contributor. The UK National Psychiatric Morbidity Survey suggests that simply forgetting to take medication is a more frequent cause of non-adherence than AEs.
• The risk of side effects varies with demographics. The same UK survey found – perhaps against expectations – that non-adherence due to AEs is more common in younger than in older patients.
• Data show that physicians can decrease discontinuation rates by discussing AEs with their patients.
• Side effects leading MDD patients to drop-out of SSRI therapy are more common in the first three months of treatment than in the second three months of treatment.
• In assessing whether an AE is likely to be drug-related, consider the plausibility of any proposed causal connection. Could what we are seeing be explained by
After years of thinking it was “someone else’s problem”, Professor McIntyre now believes that attending to patients’ physical health is as much a part of good psychiatric practice as seeking to relieve mental distress.

the drug’s known mechanisms of action? And does the timing fit with causality? This point prompted a second cartoon in which an elderly male tells his wife “I’ve been taking this drug for fifty years and I’m going to sue. Its side effects have made me wrinkled, fat and bald.”

• Expectations influence outcome. When MDD patients were warned in advance about specific side effects of SSRIs, they were 1.5 times more likely to experience mild-moderate events than patients who were not given such information in advance. Interestingly, though, there was no priming effect on the incidence of severe side effects.

• The role of expectation is nowhere more evident than in the nocebo effect: inert substances too can prompt AEs. Some placebos are certainly worth avoiding. Barsky and colleagues drew attention to the high rate at which placebos lead to the reporting by patients of non-specific side-effects. Among the AEs that appear with high frequency in the placebo arms of antidepressant trials are headache, nausea, sedation, nervousness and anxiety. Among the factors linked to this phenomenon, Barsky et al identified prior experience to medications that caused somatic symptoms, anxiety, depression and the tendency to somatise.

• Apparent side effects can be due to normalisation of function. Some patients who have lost weight because of depression put it back on when they start to feel better, entirely independently of any drug they are taking.

This theme was taken up by Professor McIntyre. Psychotherapy also causes weight gain, he noted.

But for some patients weight gain is drug-induced and unwelcome and can actually worsen the psychiatric con-

dition we are trying to treat. Associated inflammatory and insulin-related metabolic problems are likely to contribute to cognitive dysfunction and possibly to the eventual development of dementia. This is quite apart from the risk of cardiovascular ill-health associated with increasing obesity and the development of central adiposity.

After years of thinking it was “someone else’s problem”, Professor McIntyre now believes that attending to patients’ physical health is as much a part of good psychiatric practice as seeking to relieve mental distress.

People with mental health problem are generally physically less active than those not experiencing such difficulties. But meta-analyses show that non-pharmacological behavioural interventions can both prevent drug-related weight gain and lead to weight reduction in those who have added kilos as a result of treatment. He admitted that not many of his patients had been persuaded to go to the gym, but some had successfully been encouraged to get off the bus a stop or two before the hospital and walk the last stretch.
Thomas Insel’s novel proposal for research criteria based on behaviour and neurobiology suggests that we should identify the neural circuitry underlying mental disorders, detect the earliest manifestation of illness or risk of it (the equivalent of cancer in situ) and pay attention to disease domains. These include those associated with negative valence (acute threat and fear), positive valence (reward and learning), cognitive systems, and social processing.

In the case of depression, we have tended to ignore cognitive deficits. In part this is due to the idea that neuropsychological testing is time-consuming, in part to the belief that any such problems disappear with resolution of depression, and in part to the idea that there is little we can do about them. But all of these ideas should be challenged, Professor Sidney Kennedy (St Michael’s Hospital and University of Toronto, Canada) told a lunchtime meeting. In particular, we should reject the idea that cognitive impairment disappears with treatment for depression. It doesn’t.

One of the most important ways we have moved forwards is in recognising that cognition and its impairment in depression is directly associated with functional outcome and, in particular, with difficulties in returning to work and family life. According to Lee et al, impaired executive function and difficulties in memory at baseline among young depressed patients predict around 50% of the variability in outcome at two years.

Studies using the Cantab neuropsychology battery showed significant deficits in executive function and memory in MDD patients in remission. There is decline in memory with each episode of depression and this is associated with reduction in volume of the hippocampus. Compared with controls, structural MRI shows that cortical thinning is evident in MDD patients. This is associated with inattention and poor visual memory for social stimuli.

There are now cognitive test batteries that can be completed in 10-15 minutes and some can be self-administered while patients wait to see their doctor.

The deficits found most consistently in patients with major depression are in executive function, working and episodic memory, and processing speed. It has become clear that treatment of depression does not simply make associated pseudodementia go away.

In terms of treatment, assessment of transcranial magnetic stimulation is in its early days. But pilot studies suggest that cognitive remediation therapy, which uses behavioural strategies – including computer games – to improve areas of particular impairment -- can make a difference, as shown by the work of Christopher Bowie. So too can our choice of antidepressant, since drugs differ in their effects on cognitive symptoms in depression.

Brain imaging allows exploration of the neural circuitry involved and suggests ways in which therapy may improve neurocognition. This is highly relevant given the outcomes that depressed patients want from treatment. The work of Zimmerman et al reminds us that depressed patients prioritise positive mental health (optimism and vigour), feeling like their normal selves, and a return to their usual functions at work and home. Absence of the symptoms of depression per se came sixth on the list.
The APA runs a Distinguished Psychiatrist Lecture Series and one of this year’s topics was the close relationship between depression and obesity. Professor Julio Licinio trained as both a psychiatrist and an endocrinologist and is therefore more than qualified on the topic. Here are some highlights from his keynote lecture ‘Depression and Obesity: the clinical and research interface of two modern diseases’.

Old diseases, posing new problems. That’s how Prof Licinio, Director of Translational Medicine and Head of the Mind and Brain Theme at the South Australia Health and Medical Research Institute, Flinders University in Adelaide Australia, introduced depression and obesity.

He highlighted multiple reasons why these conditions merit joint consideration and common study. The diseases frequently coexist and there can be a two-way causal relationship: being obese can lead to depression and having depression can lead to obesity. Brain circuitry controlling mood and food intake are intimately linked, and indeed Prof Licinio said he believes that many of the pathways important to these disorders are one and the same.

**Much in common**
Prof Licinio reminded the audience of the prominence of these conditions in modern society. He said headlines frequently draw attention to skyrocketing rates of obesity, and he pointed out that depression is increasingly seen and diagnosed at younger and younger ages.

According to Prof Licinio, obesity and depression are far more intertwined than is widely appreciated. While sedentary-life-styles and an obesogenic food environment are facts known to contribute to the obesity epidemic, Prof reminded the audience that over-eating is often a form of self-medication for mood disorders such as depression.

Prof Licinio said both conditions may be a consequence or manifestation of chronic stress, where hypothalamic control on glucocorticoid and cortisol levels becomes deranged.

Prof Licinio described some of clinical and scientific research that is trying to piece together common mechanisms in order to understand relationships between depression and obesity. He has studied the so-called “satiety” hormone leptin - produced by adipose cells and involved in moderating food intake – looking at families with rare genetic conditions of leptin deficiency and showing that leptin replacement therapy can reverse the severe obesity that characterizes these cases. He described studies in animal models which suggest that leptin may help down-regulate chronic stress and support neurogenesis in the hypothalamus. The audience also heard about research into the role of cortisol and immune mediators in mood disorders.

Prof Licinio said that pharmacogenetic studies looking at phenotypes and genotypes in different diseases not only help identify potential new drug targets but may help highlight common ground between depression and obesity. And he added his hopes that genomics and exon genotyping will provide clues that can be used to mount what he called a “multifrontal” war on psychiatric illnesses.
Have you ever wished for a few words of wisdom to inform your thinking and guide practice-decisions around management of depression? During the APA we grabbed a minute of time with three experts to get some knowledgeable thoughts on cognitive function in patients with depression.

**Is CBT – which requires complex cognitive processes – appropriate for depressed patients with severe cognitive dysfunction?**

Prof Wittchen said: It depends what you understand as falling under the term CBT. There are some therapies that might be much too complex for patients to work with when they are severely depressed. But simple forms of behavioral therapies like behavioural-activation therapy can be really helpful in the most severe stages of depression.

**Blowing hot and cold**

**How important is the distinction between hot and cold cognition when considering cognitive dysfunction in depression?**

Prof Wittchen said: I think for clinicians the distinction between hot and cold cognitions is a useful reminder to explore the patient’s functioning in greater detail. Take the cold cognitions for example - such as attention, memory and concentration - these are necessary to maintain more complex cognitive structures such as making decisions, following-up plans and putting them into action. These cold cognitions are a prerequisite for the hot cognitions which actually involve emotion, affect and feelings as well.

**When combining pharmacological therapy with cognitive behavioural therapy (CBT), which antidepressants are most efficacious and what is the most effective sequence of therapy?**

Prof Wittchen said: Well there are almost no studies that tell us what types of antidepressant are best combined with CBT. We all know that adding CBT on top of drug treatment is beneficial and might produce better and more stable results in the long run.

**Testing, testing…**

**There are a number of tests designed to measure domains of cognitive function in depression – can you provide guidance on which tests to use?**

Dr Harrison said: There are lots of domains of cognition we could look at – episodic memory, working memory, attention. If I had just 10 minutes with a patient, I’d be tempted to use a version of the digit-symbol-substitution test, which tests lots of areas of cognition, so if there is a problem, it’s very likely to detect it. Another option would be to use working-memory tests. If these are computerized – I’d chose a one- or a two-bank, while if the test needs to be paper-and-pencil based, I’d suggest digits-backwards. Then, I’d look at attention using a computerized test like choice-reaction-time.

**Sensitive to criticism**

**To what extent is response to negative feedback state-related?**

Prof Harmer said: Once a patient has received negative feedback on a task, or noticed that they have made an error, they then go on and make further errors in that task. And that seems to be something quite specific to depression. To some extent, this has been investigated only when depressed patients are currently ill, so we don’t know if it is state or trait-related. But some evidence suggests it may be trait-related in that it’s also seen in people that are at heightened risk of developing depression.
Sweet dreams

What is the impact of insomnia on cognitive function in depression, both during the acute phase and on the residual cognitive symptoms during remission?

Prof Wittchen said: Sleep and the quality of sleep has a tremendous effect on cognition – how you can memorize, work, concentrate and function. And particularly in a depressive episode – sleep disturbances heavily affect cognitive function. So it’s important to address sleep disturbance as well as cognitive function.

Who we spoke to

Professor Hans-Ulrich Wittchen
Chair of the Institute of Clinical Psychology and Psychotherapy at the Technische Universität, Dresden, Germany

Dr. John Harrison
Honorary Senior Lecturer at the Department of Medicine, Imperial College London, UK

Professor Catherine Harmer
Professor of Cognitive Neuroscience in the Department of Psychiatry, Oxford University, UK

Want more of the same?

More from these experts — all of whom are members of the THINC Task Force — can be found @THINCcognition.com
Patients with major depressive disorder that appears not to respond to antidepressant therapy are a broad group. According to Dr. Nemeroff, as many as 25% of these patients are incorrectly labelled as having treatment-resistant depression. He said there are some patients for whom it is a case of finding the right treatment and ensuring the treatment is given at an adequate dose. Patients like these are not strictly-speaking treatment-resistant but may be fast metabolizers, may be slow responders, or may respond better to trial of an antidepressant of a different class.

Look for zebras
Dr. Nemeroff also reminded his audience that non-response to treatment might be a sign that depression is secondary to another, occult or undisclosed disorder requiring correction and management. This could include occult substance or alcohol abuse and he advised exploring possible cause not only with the patient but also through talking with family and partners if relevant. He also said failure to respond well to an antidepressant in some cases should prompt review the psychiatric diagnosis. As he put it: “if you hear the sound of hoofs and can’t see any horses – look for zebras”.

Giving it time
Taking the time in consultations to talk to all patients about their antidepressant therapies is crucial, according to Dr. Nemeroff. He said that another very common reason for apparent treatment failure can be non-adherence. And he had some tips for delegates. He said that rather than covering potential adverse effects of treatment right at the end of a consultation, clinicians should cover that topic earlier, so that the patient doesn’t leave an appointment with their head full of the potential downsides of treatments rather than the potential benefits.

Dr. Nemeroff also advised that once patients with depression are in remission, psychotherapy – which he described as being a real biological intervention – offers another tool to help keep them there.

He had lots of advice on a plethora of options and ways to manage patients who could be described as having treatment-resistant depression and used a patient case example to interact with the audience and hear their thoughts on patient management.

The session ran over time as delegates lined up with questions about myriad practical aspects of patient care – showing that APA interactive sessions are just that.

* Dr. Nemeroff is the Leonard M. Miller Professor and Chair, Department of Psychiatry and Behavioural Sciences at the University of Miami, Miller School of Medicine, Florida.

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