

Volume 1, Issue 2
May 2010

In this issue

What is CIMR

Welcome: Dr. Sinha and Dr. Downar

What's New in Depression Research?

Biomarker Discovery for Early Onset of Antidepressant Response

Interview: Dr. Alastair Flint, Head of Geriatric Psychiatry

Contact: The Centre for Integrative Mood Research

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Founding Members of CIMR:

Dr. Sophie Grigoriadis
Dr. Sidney Kennedy
Dr. Roger McIntyre
Dr. Sagar Parikh
Dr. Franco Vaccarino



What is the CIMR?

The CIMR has recently been established at University Health Network to promote the understanding of depression and mood disorders; to develop innovative evidence-based therapeutic interventions, and to disseminate and apply this knowledge to the general public, the health care community, and policy makers.

We are currently accepting referrals for consultation and possible ongoing collaborative care. Patients may have the opportunity to participate in clinical trials. Please contact: Wilma.aranha@uhn.on.ca (416-340-3888) at Toronto General Hospital for depression-related referrals, and Bernadette.defreitas@uhn.on.ca (416-603-5800 x 6508) at Toronto Western Hospital for referrals related to bipolar disorder.

As part of our ongoing commitment to education, the CIMR is proud to sponsor educational events throughout the year.

We held our first Education Event "Neurostimulation for Psychiatrists" in Toronto April 30 and May 1, 2010. The event was very successful and participants learned about the latest in Transcranial Magnetic Stimulation, Deep Brain Stimulation, and Electroconvulsive Therapy. A highlight of the workshop was the "hands on" breakout sessions with the devices.

Our next event on "Women's Mental Health" is scheduled for Fall 2010. Contact susan.rotzinger@uhn.on.ca for further details.

NEUROSTIMULATION FOR PSYCHIATRISTS:

A Practical Guide to Neuroimaging, TMS, ECT and DBS



April 30th and May 1st, 2010

University of Toronto
Faculty Club

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Welcome Dr. Sinha



Dr. Smit Sinha completed medical school and psychiatry residency at the University of Alberta. He completed a NIMH research fellowship in anxiety disorders, and then was Assistant Professor in the Department of Psychiatry at Columbia University. He was the recipient of a Clinical Scientist Career Development Award from the National Institute of Mental Health focusing on the neuroendocrinology of panic disorder. He is interested in advancing neurobiological study and developing novel treatments for the breadth of anxiety disorders, depression, and mixed anxious-depressive states.

Dr. Smit Sinha completed medical school and psychiatry residency at the University of Alberta. He completed a NIMH research fellowship in anxiety disorders, and then was Assistant Professor in the Department of Psychiatry at Columbia University. He was the recipient of a Clinical Scientist Career Development Award from the National Institute of Mental Health focusing on the neuroendocrinology of panic disorder. He is interested in advancing neurobiological study and developing novel treatments for the breadth of anxiety disorders, depression, and mixed anxious-depressive states.

Welcome Dr. Downar



Dr. Jonathan Downar will be joining the CIMR in July 2010. Dr. Downar obtained his PhD in neuroimaging at the University of Toronto in 2002 before completing his medical degree at the University of Calgary in 2005. He is currently in the final year of his Psychiatry residency at the University of Toronto. He also recently completed a concurrent fellowship in neuroeconomics (the neuroscience of decision-making) at Baylor College of Medicine in Houston, Texas. Alongside his psychiatry training, he has conducted research on the functional neuroanatomy of the cortex, and on the neural basis of effective decision-making in experienced physicians. At present, his research interests are in using neuroimaging techniques to identify new targets for brain stimulation treatments in mood disorders.

Dr Downar also has a strong interest in public science education. He served as a screenwriter and scientific advisor on the IMAX film "Wired to Win: Surviving the Tour de France". With co-author Dr. David Eagleman, he is also in the process of completing an undergraduate textbook of cognitive neuroscience, scheduled for publication by Oxford University Press in 2011.

Dr. Jonathan Downar will be joining the CIMR in July 2010. Dr. Downar obtained his PhD in neuroimaging at the University of Toronto in 2002 before completing his medical degree at the University of Calgary in 2005. He is currently in the final year of his Psychiatry residency at the University of Toronto. He also recently completed a concurrent fellowship in neuroeconomics (the neuroscience of decision-making) at Baylor College of Medicine in Houston, Texas. Alongside his psychiatry training, he has conducted research on the functional neuroanatomy of the cortex, and on the neural basis of effective decision-making in experienced physicians. At present, his research interests are in using neuroimaging techniques to identify new targets for brain stimulation treatments in mood disorders.

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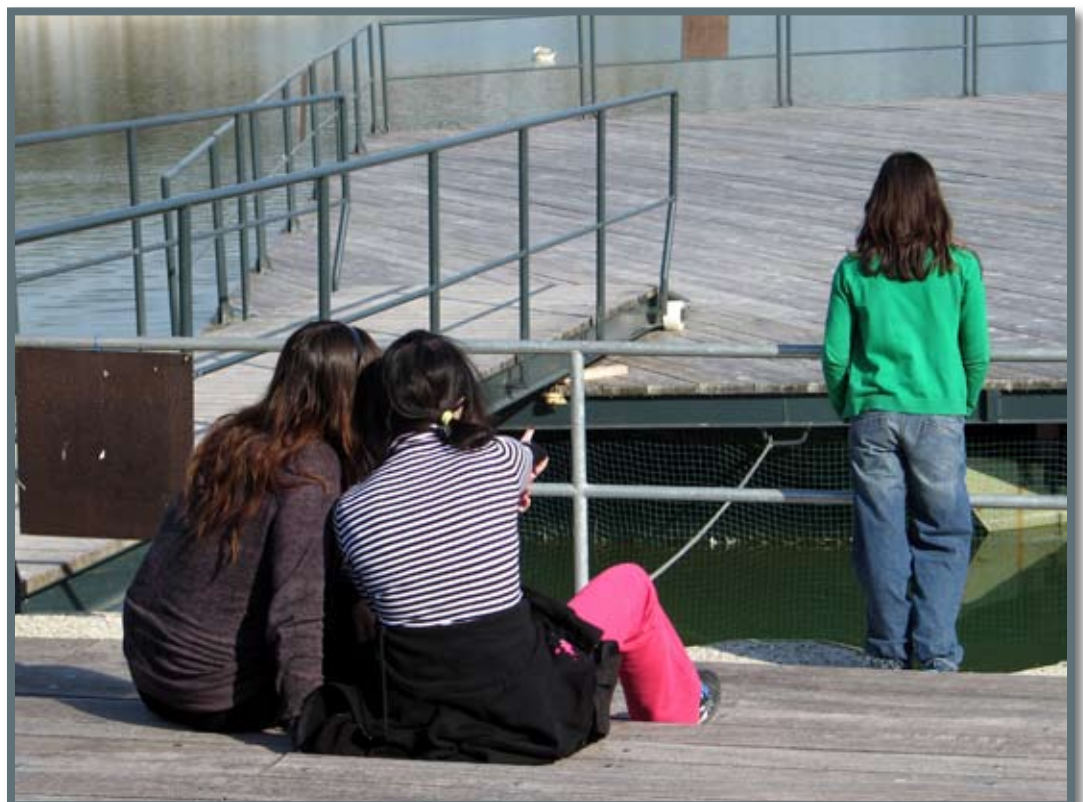
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What's New in Depression Research?

Biomarker Discovery for Early Onset of Antidepressant Response

Major Depressive Disorder (MDD) is a serious and debilitating psychiatric illness that will affect 8% of Canadians in their lifetime. Clinically significant antidepressant response can typically take several weeks following the initiation of drug treatment, as measured by standardized rating scales. Although early improvement in symptoms can be seen after 1-2 weeks of treatment, and may be an indicator of remission, full remission can take 8 weeks or longer (Lam et al., 2009). If remission is not achieved within this time frame, then switching to a different antidepressant medication, or adding-on another medication is recommended (Lam et al., 2009), and the waiting begins again. In a large-scale study of antidepressant treatment, only 30% of patients demonstrated remission after the first treatment (Gaynes et al., 2009). Waiting for treatment response can be a challenging time for patients and physicians alike, and is a time during which patients may discontinue treatment due to lack of response. Identifying early indicators of treatment response would help to optimize treatment, and is an active area of current research.

As there is currently no biological diagnostic test for MDD, scientists are looking for other biologically-based measures that might correlate with treatment



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response. Such “biomarkers” may help in the early prediction of treatment response, and enable more rapid optimization of treatment personalized to an individual patient. Studies are now showing that differences in physiological or personality measures can be detected either prior to treatment, or during treatment, that may give even earlier indications of treatment response than can be detected by either observer-rated or self-report measures. For example, using the neuroimaging technique of Positron Emission Tomography (PET), scientists were able to discover that patients that failed to respond to an adequate trial of either cognitive behaviour therapy or venlafaxine, had increased metabolic activity in a specific region of the brain (Konarski et al., 2009). In another study, scientists identified that the personality trait of Harm Avoidance is associated with depression, and mediates the response to serotonergic antidepressants (Quilty et al., 2010).

Dr. Peter Giacobbe, Staff Psychiatrist at University Health Network, is currently conducting studies to assess possible early indicators of antidepressant efficacy using technology that can measure visual attention to pictures of varying emotional intensity. Dr. Giacobbe is enrolling patients with MDD who will be treated with the antidepressant drug duloxetine (Cymbalta®), and assessed weekly both with clinical rating scales and using eye tracking software to assess visual attention to images on the computer. Eizenman and colleagues (Eizenman et al 2003; Yu and Eizenman, 2004) have developed and validated a system for tracking the precise location and time spent focusing visual attention on images displayed on a computer screen. They found that subjects with depressive disorder spent significantly more time looking at the images depicting a sad or dysphoric theme, than did healthy controls.

Negative attentional bias is the tendency to orient attention to negative information. This is seen in terms of attention to negative facial expressions, images, words, and the memory for these items. People with depression have a significant negative attentional bias, which is thought to contribute to the initiation and perpetuation of the mood disorder. Recently, researchers have shown early improvements in physiological measures associated with the negative attentional bias, preceding even the cognitive awareness of improvements in mood. Following a single dose of the antidepressant medication reboxetine, depressed patients showed a reversal of their pre-treatment deficit in recognition of positive facial expressions, as well as response to and memory for positive personality adjectives (Harmer et al., 2009). These changes occurred within hours of drug treatment, and without any subjective effects on mood. Thus, changes begin to occur early on in treatment, which are below the level of clinical detection, and which may be predictive for treatment outcome.

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Dr. Giacobbe's hypothesis is that a shift away from the negative attentional bias in depressed individuals will precede the clinical improvement in symptoms, but only in those individuals who eventually show a significant reduction in depression scores after the 6-week drug treatment period. If this is the case, then changes in selective visual attention could eventually be used as a biomarker of early treatment response. Such information would greatly enhance the ability to treat patients more rapidly, and may help our understanding of the biological causes of depression. For more information on Dr. Giacobbe's work, please contact him at peter.giacobbe@uhn.on.ca



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Interview: Dr. Alastair Flint, Head of Geriatric Psychiatry

Q: What is psychotic depression, and how common is it?

Psychotic depression is major depression with associated psychotic features. Whilst the DSM-IV definition of psychotic depression allows for the presence of delusions or hallucinations, most experts agree that it is rare for hallucinations to occur without delusions in this disorder. Thus, the term 'delusional depression' has sometimes been used synonymously with psychotic depression. Whilst psychotic depression is nearly always severe, in terms of symptoms and impairment, severity alone is not sufficient to make the diagnosis — psychotic features must be present. Interestingly, there are many people with severe depression who never become psychotic. Persons with psychotic depression presumably have a distinct biological vulnerability to experience psychosis as a part of their mood disorder.

Approximately 15-20% of persons with major depression have a lifetime history of psychotic features. In community-based epidemiological surveys, the 1-6 month prevalence of psychotic depression is approximately 0.5%, which is comparable to bipolar 1 disorder or schizophrenia. In addition to severity of symptoms, psychotic depression is associated with a high rate of suicide attempts, severe functional impairment, and a high rate of relapse. For these reasons, it accounts for 20-25% of cases of major depression in psychiatric inpatient settings, and up to 45% of cases of major depression amongst older psychiatry inpatients.

Q: What is the recommended treatment for psychotic depression?

Based on the results of randomized controlled trials, expert guidelines recommend either electroconvulsive therapy (ECT) or the combination of antidepressant and antipsychotic medications to treat psychotic depression. Research conducted in academic centers has found that ECT can result in a high rate of remission of psychotic depression (sometimes above 80% remission), when it is given as the first line of treatment. However, the use of ECT is limited by several factors, including a high rate of relapse following completion of ECT, markedly lower rates of remission in non-academic centers, significant disparities in its availability, and the fact that many patients prefer pharmacologic treatment, because they find the concept of ECT and the potential side effect of cognitive impairment unacceptable. As a result of these limitations, the pharmacologic treatment of psychotic depression is common. The recently completed NIMH-funded Study of the Pharmacotherapy of Psychotic Depression (STOP-PD) was the first study to examine the efficacy and tolerability of combined second-generation antidepressant and antipsychotic drugs in the treatment of

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psychotic depression. Close to 70% of participants who completed 12 weeks of treatment with combined sertraline and olanzapine experienced remission of both depressive symptoms and psychosis. However, the rate of attrition during the study, primarily due to severity of illness and the need to switch treatment to ECT, was quite high, indicating that both ECT and pharmacotherapy have a place in the management of this disorder.

A current conundrum in the treatment of psychotic depression is how to keep patients well once symptoms remit. As mentioned, there is a high rate of relapse following ECT. Various strategies (such as continuation of ECT, combining an antidepressant with an antipsychotic, or combining an antidepressant with lithium) have been studied for prevention of relapse after ECT, but none of these strategies are very efficacious in this regard. In addition, we do not know how long to continue antipsychotic medication once psychotic depression responds to a combination of an antidepressant and antipsychotic: this is a significant issue, since the premature discontinuation of the antipsychotic could place the patient at risk of early relapse, whilst prolonged exposure to the antipsychotic places the patient at risk of long term adverse effects. There is a pressing need for further research into the continuation treatment of psychotic depression.

Q: You recently published a paper indicating that the diagnosis of psychotic depression is often missed. Why do you think this happens, and what should physicians and psychiatrists be doing differently?

In the study that you mention, we examined to what extent psychotic depression (confirmed by research interview) is detected in routine clinical practice. The study was limited to 4 academic medical centers. Twenty seven percent of cases of psychotic depression were misdiagnosed; in each instance the patient was diagnosed with an affective disorder, but the psychotic features (namely delusions) were missed. There was



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not a single case where psychotic depression was misdiagnosed as another psychotic disorder, such as schizoaffective disorder or schizophrenia. Thus, the challenge in diagnosing psychotic depression is to determine whether the worries, ruminations, and somatic concerns, that are so commonly associated with depression, are delusional. This can take time, since it involves careful evaluation of the patient's thought content, reasoning, and logic. Thus, being vigilant to the possibility of delusions and taking the time to carefully evaluate the patient's thinking are critical to making the diagnosis.

Q: How is psychotic depression different in young versus older adults, in terms of the presentation of the illness and its treatment?

For unknown reasons, the frequency of psychotic depression increases with age. The presentation of psychotic depression in older adults can be surprisingly stereotypical: the onset of an episode is often abrupt, with rapid progression to severe symptoms and significant functional decline; the person usually has significant psychomotor retardation or agitation or a mixture of the two; the delusions are usually mood-congruent; and the same delusional themes frequently recur from one depressive episode to the next. In younger patients, the presentation may be less consistent. Specifically, there is less consistency with respect to psychomotor change, the congruence of the delusions with mood, and the severity of acute functional change. In some instances, the phenotype of psychotic depression in younger adults may eventually progress to bipolar affective disorder or schizoaffective disorder, whereas this is not the case in older adults. This may be one reason why the clinical presentation of psychotic depression in younger adults may be less stereotypical than in older adults.

ECT and combination pharmacotherapy are effective in both younger and older adults with psychotic depression. However, older patients are more likely to receive ECT than younger patients, due to the fact that they are more vulnerable to the acute physical and functional effects of psychotic depression, and therefore may be less able to 'wait out' a trial of pharmacotherapy. Nevertheless, of those patients who are suitable for pharmacotherapy, the STOP-PD trial found that rates of remission were comparable between younger and older individuals.