

Mood and Anxiety Disorders Rounds™

A PHYSICIAN LEARNING RESOURCE FROM THE CANADIAN NETWORK FOR MOOD AND ANXIETY TREATMENTS

The Canadian Biomarker Integration Network for Depression (CAN-BIND): Looking Deeper into Major Depressive Disorder

BY SUSAN ROTZINGER, PhD, AND SIDNEY KENNEDY, MD, FRCPC, MBBS, ON BEHALF OF THE CAN-BIND TEAM

The increasing prevalence of depressive disorders and the limited efficacy and escalating costs associated with current treatments led a group of physicians at the University of Toronto to create CAN-BIND. Their vision is to define the biological signatures of currently uncharacterized subtypes of major depressive disorder (MDD) in order to provide an accurate and rapid diagnosis that can determine treatment selection. This will be accomplished by systematically collecting individual data across a wide range of biological and environmental factors in an effort to classify depressive subtypes and identify biomarkers. Enrolment is projected to be 400 MDD patients from 8 major Canadian centres as well as a healthy control population. This issue of *Mood and Anxiety Disorders Rounds* describes the rationale behind the creation of CAN-BIND, its educational partners, the protocol and aims of CAN-BIND-1, and the clinical assessments that will be used to identify and evaluate potential biomarkers of treatment response. Contact information for interested participants is also provided.

Biomarkers of the subtypes of depression and treatment response have been the subject of decades worth of research efforts. Given the complexity and diversity of symptoms and outcomes in major depressive disorder (MDD), it is unlikely that a single marker (eg, genetic, protein, imaging, or a clinical feature) can reliably predict and classify depression subtypes or guide treatment. Since each person with MDD is different, family physicians and psychiatrists often find it challenging to decide which treatment best matches the symptoms of the individual patient. There is growing consensus that MDD is best viewed as a group of depressive disorders, each with different contributing etiological pathways which require individualized treatment decisions. This realization highlights the need for large, multisite, multifocused, collaborative groups with the resources to gather and integrate a wide range of standardized data from a large number of patients. The Canadian Biomarker Integration Network for Depression (CAN-BIND) is a unique group in Canada that addresses this need.

Background

Response rates to different drug treatments are approximately 50%, while remission rates are usually <40% after 6–8 weeks of treatment.¹ High rates of treatment resistance are a major roadblock to successful treatment outcome for many patients. Because of the high prevalence and high levels of disability associated with MDD, there is a significant social and economic impact.^{2,3} In addition, MDD is associated with a predisposition towards obesity and other metabolic disorders, increased medical comorbidities, reduced adherence to medical treatment, and higher mortality rates.⁴ There are currently no biomarkers to identify subtypes of MDD that can help guide treatment selection. Despite major advances in neuroscience and biological psychiatry, treatment using these techniques has not yet been integrated in a clinically useful way to guide treatment selection.

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Canadian Network for Mood and Anxiety Treatments

Education Office
Room 9M-329, Toronto Western Hospital
399 Bathurst St, Toronto, On
CANADA M5T 2S8

CANMAT – or the Canadian Network for Mood and Anxiety Treatments – is a federally incorporated academically based not-for-profit research organization with representation from multiple Canadian universities. The ultimate goal of CANMAT is to improve the quality of life of persons suffering from mood and anxiety disorders, through conduct of innovative research projects and registries, development of evidence

Imaging markers

Brain imaging studies have revealed differences in structure and function between MDD patients and controls; however, the best way to use these results to guide clinical treatment remains elusive.⁵ Brain imaging techniques can be used to measure functional connectivity between brain regions and provide information about the activity in defined neural circuits; functional imaging studies examine brain changes while subjects perform a task in the scanner.⁶ In MDD, connectivity is decreased in some regions and increased in others when compared with healthy controls,⁷ and these changes are associated with episode duration.⁸ In order to move this area of research forward, clinical studies are needed to determine the differences in resting state functional connectivity between treatment responders and nonresponders and whether these differences can predict antidepressant response. These studies are also useful in assessing altered emotional processing (eg, increased attention to negative stimuli) in MDD⁹ that can be predictive of treatment response.¹⁰

In addition to functional changes, structural differences in brain regions have also been observed in MDD. Regional grey matter deficits in frontal lobe regions¹¹ and in subcortical structures¹² have been found in MDD patients as compared to healthy controls. For example, smaller hippocampal volumes are associated with worse clinical outcomes, as well as longer illness duration and multiple depressive episodes.^{13,14} A history of trauma or negative life events is also associated with smaller volumes in specific brain regions in both healthy controls and MDD patients.^{15,16} These findings support an integrative approach that connects life events and clinical assessments with neuroimaging data. White matter fibre tract abnormalities have also been demonstrated in MDD using diffusion tensor imaging (DTI), which allows visualization of white matter fibres and patterns of connectivity. DTI has consistently shown decreased white matter tract integrity in regions that correspond with grey matter abnormalities, such as connections to other cortical and subcortical (amygdala and hippocampus) areas.¹⁷⁻¹⁹ Few studies have assessed the relationship between these abnormalities in white matter and treatment response and even fewer have examined integrated functional and structural neuroimaging data. In addition, many of the investigations that were performed had small sample sizes. This highlights the need for adequately powered studies to better understand how imaging biomarkers can be used clinically to predict treatment response.

The CAN-BIND study will integrate structural, functional and DTI measures along with electroencephalographic (EEG) data to gain a more complete picture of early neurobiological and neurophysiological markers of treatment response.

Molecular markers

Early investigation into the genetics of MDD and antidepressant response examined genetic variations in candidate genes and initially provided significant evidence for the association between some genes and treatment outcome. However, there is now a broad consensus that genetic polymorphisms explain only a small fraction of the total variance in drug

response among individuals with MDD. Instead, the expression of genes is likely to be more important in terms of changes in functional activity. Therefore, investigating gene functional changes associated with antidepressant response, as well as the molecular factors regulating these changes, will likely provide valuable information in identifying valid biomarkers. This line of study will also shed light on the mechanisms involved in successful response to treatment and potentially identify novel treatment targets for MDD.

Members of our research team have found evidence that the genes involved in immunological and inflammatory processes and in neurotrophin signaling are differentially regulated in response to citalopram.^{20,21} The CAN-BIND study will expand on previous research focusing on molecular biomarkers of antidepressant response and carry out a series of complementary large-scale studies with sufficient power to generate meaningful results that can better inform treatment approaches based on biological markers.

Proteomics – the study of the protein products of gene expression – has been used widely in other fields of medicine and has potential to help define phenotypes in psychiatric disorders.²² While a single blood-based biomarker is unlikely to be discovered, panels of biomarkers based on known dysregulated pathways, including measures of immune, metabolic and hormonal function, may hold promise.²³

The CAN-BIND Network

Rationale

Beyond a categorical symptom-based approach to diagnosis, there is growing recognition that variations in the way emotional and cognitive neurocircuits perform in the resting state and in response to standardized challenge paradigms, as well as findings linking altered biochemical/molecular products to depression, provide an additional level of analysis that may identify subtypes within the broader categorical construct of MDD.^{24,25} Identifying homogeneous subtypes within MDD patients can help in the development of biomarkers and, conversely, the availability of biomarkers can help in identifying patient subgroups. Large-scale collaborative datasets with standardized measures that can be shared and compared between and among researchers will be a significant step towards this goal.²⁶ A further necessity, given the limited knowledge of the molecular basis of psychiatric illness, is an unbiased approach to biomarker discovery.²⁷ Multimodal studies combining information from clinical, imaging, and molecular domains have the potential to develop a model with adequate specificity and reliability to have a meaningful impact on predicting treatment response.²⁸⁻³⁰

CAN-BIND overview

CAN-BIND³¹ is a joint initiative among researchers at 8 Canadian universities (Table 1) and has collaborative partnerships with the Ontario Cancer Biomarker Network and the Ontario Brain Institute.

The vision of CAN-BIND is to define the biological signatures of currently uncharacterized subtypes of MDD to provide an accurate and rapid diagnosis that can determine treatment selection (Figure 1). Using a bioinformatics approach to integrate clinical, imaging, and molecular data, researchers hope to identify meaningful constellations of fea-

Table 1: Canadian universities participating in CAN-BIND

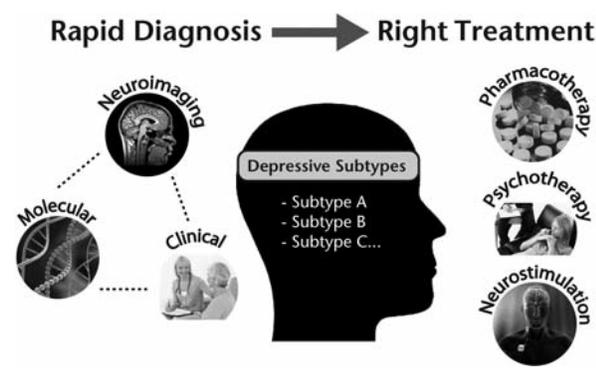
- University of Toronto
 - University Health Network and Centre for Addiction and Mental Health
- McMaster University (Hamilton)
- Queen’s University (Kingston)
- University of Guelph
- University of Ottawa
- McGill University (Montreal)
- University of Calgary
- University of British Columbia (Vancouver)

CAN-BIND = Canadian Biomarker Integration Network for Depression

tures that would then act as biomarkers that differentiate subtypes of depression and direct treatment choice. This will be an ongoing program of studies with both discovery and validation components. Our first study is designed to identify biomarkers for treatment response to pharmacotherapy in MDD. During the next 5 years, the CAN-BIND platform will be used to expand focus to include depression in other populations and to other treatment modalities (eg, CAN-BIND-2: neurostimulation).

CAN-BIND-1

The first study, CAN-BIND-1, is underway at 6 Canadian sites (Table 2). Neuroimaging and data analysis methods have been developed and tested^{32,33} that can be used across all sites. Standard operating procedures for the collection of biospecimens are in place and standardized clinical assessments have been selected and implemented for electronic data capture and transmission to BrainCODE, an integrated database supported by the Ontario Brain Institute that will facilitate complex bioinformatic analyses and high performance computing. BrainCODE is deployed at the High Performance Computer Virtual Lab (www.HPCVL.org) data centre in Kingston, Ontario, which supports regulatory-compliant (eg, Code of Federal Regulations Title 21 [21 CFR] Part 11, Health Insurance Portability and Accountability Act [HIPAA], Personal Information Protection and Electronic Documents Act [PIPEDA]) processes for securing privacy of healthcare data.

Figure 1: CAN-BIND Vision**Table 2: CAN-BIND contact information**

Site and principal investigator	Contact
University Health Network	
Dr. Sidney Kennedy	(416) 340-4800, ext. 8839
Centre for Addiction and Mental Health	
Dr. Arun Ravindran	(416) 535-8501, ext. 36347
McMaster University	
Dr. Benicio Frey	(905) 522-1155, ext. 32048
Queen’s University	
Dr. Roumen Milev	(613) 548-5567, ext. 6123
University of Calgary	
Dr. Glenda MacQueen	(403) 210-7321
University of British Columbia	
Dr. Raymond Lam	(604) 822-7627

CAN-BIND has received peer-reviewed funding from the Ontario Brain Institute and the Canadian Institutes of Health Research. It has also received private-sector donations via the Toronto General and Western Hospitals Foundation (from Lundbeck Canada and Servier Canada) to establish the clinical infrastructure across 6 Canadian academic centres and cover the costs of the clinical and neuroimaging protocols. In-kind support has also been received from the Ontario Brain Institute to securely transmit and store project data in BrainCODE.

CAN-BIND is dedicated to employing an integrated knowledge translation (KT) approach through a primary partnership with the Canadian Network for Mood and Anxiety Treatment (CANMAT). KT dissemination will occur through publications, a website (www.canbind.ca), social media, national and international conference presentations, and local workshops. Specific KT objectives include:

- providing new information and ideas to mental health treatment providers, principally psychiatrists and family physicians
- engaging patients, mental health treatment providers, and the general public through social media and our website
- incorporating public and peer feedback and questions into future research directions.

CAN-BIND actively supports the training and development of clinicians, researchers, and other highly qualified personnel. The CANMAT has partnered with Pfizer Canada to offer Clinical Research Fellowship Awards to provide support to a psychiatrist as a clinical research fellow in depression studies. The interdisciplinary nature of CAN-BIND research offers enhanced learning opportunities for trainees and participating scientists and clinicians to act as members of the team and share their expertise in mathematics, genetics, proteomics, bioinformatics, physics, and clinical trials methodology.

The CAN-BIND-1 protocol

The CAN-BIND-1 study is designed to maximize feasibility and generalizability. The inclusion/exclusion criteria are

sufficiently broad to include a representative sample of outpatients who are moderately depressed (Table 3). Escitalopram was selected as the treatment for this study due to its high tolerability, minimal drug-drug interactions, and superior efficacy in MDD.³⁵ Aripiprazole was also selected for augmentation of non-responders based on its efficacy and safety.^{35,36} A randomized, placebo-controlled design was considered but not adopted because recruitment of a large “real world” sample with acceptably low drop-out rates did not favour the inclusion of a placebo arm.

Table 3: CAN-BIND inclusion and exclusion criteria

MDD patients

Inclusion criteria

- Outpatients aged 18–55 years
- Meet DSM-IV-TR criteria for a major depressive episode in MDD as determined by the MINI³⁴
- Episode duration ≥ 3 months
- Free of psychotropic medications for at least 5 half-lives (eg, 1 week for most antidepressants, 5 weeks for fluoxetine) before baseline visit 1
- MADRS score ≥ 24
- Fluency in English, sufficient to complete the interviews and self-report questionnaires

Exclusion criteria

- Any Axis I diagnosis other than MDD that is considered the primary diagnosis
- Bipolar I or II diagnosis
- Presence of a significant Axis II diagnosis (borderline, antisocial)
- High suicidal risk, defined by clinician judgment
- Substance dependence/abuse in the past 6 months
- Presence of significant neurological disorders, head trauma, or other unstable medical conditions
- Pregnant or breastfeeding
- Failure of ≥ 4 adequate pharmacological interventions (as determined by the Antidepressant Treatment History Form)
- Started psychological treatment within the past 3 months with the intent of continuing treatment
- Previously failure on or intolerance to escitalopram, and risk for hypomanic switch (ie, with a history of antidepressant-induced hypomania)

Healthy controls

- 18–55 years old
- No history of Axis I or II disorders, as determined by the MINI
- Fluency in English, sufficient to complete the interviews and self-report questionnaires

MDD = major depressive disorder; DSM-IV-TR = *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, text revision; MINI = Mini-International Neuropsychiatric Interview; MADRS = Montgomery-Asberg Depression Rating Scale

The study design is presented in Figure 2. All eligible subjects must provide written informed consent prior to participation. Baseline data are collected, including clinical assessments, blood and urine collection for molecular markers, functional and structural neuroimaging, and EEG. In Phase I (weeks 1–8), subjects with a diagnosis of MDD (moderate severity: Montgomery-Asberg Depression Rating Scale [MADRS] score ≥ 24) receive open-label antidepressant treatment with escitalopram (10–20 mg). Imaging and blood samples are collected at weeks 2 and 8, with additional blood samples for genetic analysis collected at week 4. Clinical data are collected at weeks 2, 4, and 8.

At week 8, patients are assessed for treatment response as determined by a $\geq 50\%$ reduction in baseline MADRS score. Responders remain on their effective dose of escitalopram for an additional 8 weeks. Non-responders receive adjunctive, open-label antipsychotic treatment with aripiprazole (2–10 mg). Clinical data are collected at weeks 10, 12, and 16, and blood samples are collected at week 16.

A healthy control group will be included in the study and, although not receiving treatment, they will undergo the same assessments as patients at screening, baseline, and weeks 2, 8, and 16 without receiving medication.

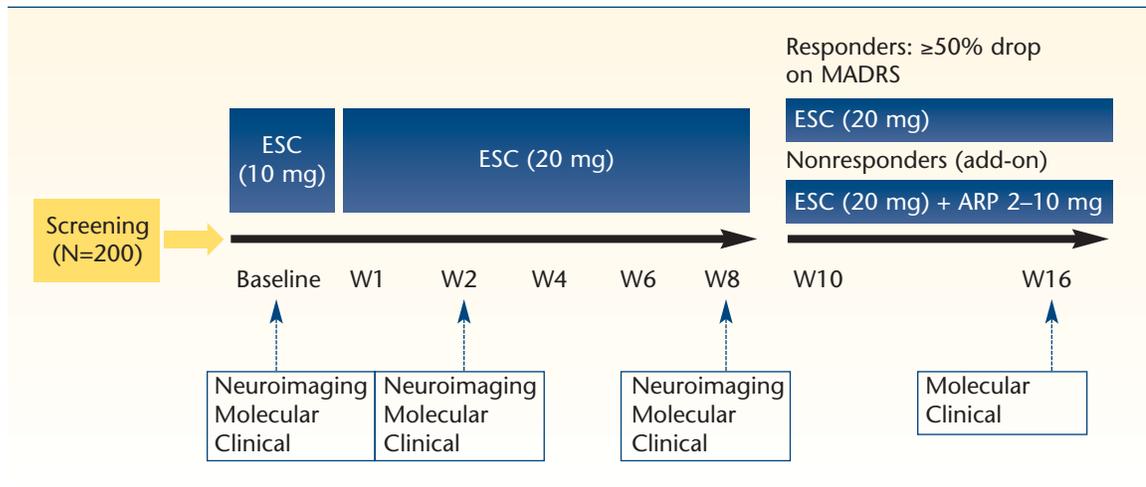
Clinical assessments in CAN-BIND-1

Diagnostic assessments will be conducted by trained clinical research staff. Demographic information will be obtained, including age of onset, number of previous episodes, medication history, and number of hospital admissions. Depressive symptoms will be assessed using the MADRS score,³⁷ one of the most widely used, clinician-rated, depression rating scales, and the Quick Inventory for Depressive Symptomatology-Self Report (QIDS-SR).³⁸ Manic/hypomanic symptoms will also be monitored. Several behavioural dimensions such as behavioural activation, personality, somatisation/anxiety, pain, chronobiology/sleep disorder, and anhedonia will be assessed. A battery of neurocognitive tests will also be collected, along with environmental assessments of stress and early life experience, adult patterns of attachment, and recent stressful life events. Data will be collected on measures of functioning and quality of life, anxiety, and medication adverse effects, including sexual function.

Neuroimaging and electrophysiology. Subjects will undergo magnetic resonance imaging (MRI) at 0, 2, and 8 weeks after beginning treatment. These time points are chosen to reflect baseline and early predictors of response, as well as the changes in brain structure and function associated with response to monotherapy. Each session will consist of a structural and functional MRI protocol. Subjects will also undergo EEG at 0, 2, and 8 weeks that will examine EEG-specific modifications during the resting state and during functional tasks.

Genomics and proteomics. Blood samples will be collected at 0, 2, 8, and 16 weeks of treatment for genomic and proteomic analyses. Pathways implicated in psychiatric illness, including those related to neurotransmitter

Figure 2: CAN-BIND-1 protocol



ESC = escitalopram; ARP = aripiprazole

function, inflammation, and neurogenesis, will be investigated. The heterogeneity of depressive symptomatology, response, and progression suggests that the underlying etiology may involve complex interactions within and among these and other systems at the level of protein, ribonucleic and deoxyribonucleic acid, and epigenetic controls that are unlikely to be understood by studying any single mechanism, protein, or gene. Consequently, multiple molecular profiling approaches will be applied, along with a comprehensive and well-established informatics platform for integrating and analyzing these data. This will provide a holistic view of the activity within and between these pathways. Furthermore, by using genomic results (eg, differential expression of a given gene in one group relative to another) to inform proteomic screening and vice versa, an interactive, fully integrated process for profiling drug response and identifying phenotypes will be achieved.

Informatics strategy. The CAN-BIND program will produce several data sets from each modality (imaging, molecular, clinical, and EEG) that will be analyzed both within and between modalities. The analyses will begin with simple univariate statistical protocols and move on to multivariate methods such as linear and logistic regression after several variable reduction steps, before applying machine learning methods (eg; support vector machines, classification and regression trees, Random Forests™, clustering, and neural nets), including novel methods developed in-house. For example, “Butterfly” is an algorithm that detects subtle differences between patient groups and returns a 2-dimensional model that captures the complex relationships between subjects by utilizing a discrete dynamical system. This greatly simplifies the analysis and reduces the chance of overfitting the data.³⁹

Conclusion

The Canadian Biomarker Integration Network has embarked on a multisite, multimodality program to identify and evaluate biomarkers of treatment response

and identify biologically meaningful subtypes within MDD. A series of controlled studies evaluating clinical, molecular, and imaging biomarkers during standardized pharmacotherapy (CAN-BIND-1), neurostimulation treatments (CAN-BIND-2), and other treatment modalities is underway. We are dedicated to an integrated KT process and invite interested researchers, physicians, study participants, and advocacy groups to contact us at the nearest CAN-BIND location (Table 2).

Dr. Rotzinger is the Clinical Research Project Manager and an Assistant Professor in the University Health Network, University of Toronto. **Dr. Kennedy** is a Professor and the Psychiatrist-in-Chief in the University Health Network, University of Toronto.

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Dr. Rotzinger is a shareholder of Protagenic Therapeutics, Inc. and is named on patents for "Teneurin C-terminal associated peptides (TCAP) and uses thereof". Dr. Kennedy has received honoraria from Servier, Eli Lilly, Spimaco, Bristol-Myers Squibb, AstraZeneca, and Lundbeck. He has received research support from AstraZeneca, Bristol-Myers Squibb, Brain Cells Inc., Clera Inc., Eli Lilly, GlaxoSmithKline, Lundbeck, and St. Jude Medical Inc. He is on advisory boards for AstraZeneca, Eli Lilly, Pfizer, Servier, St. Jude Medical Inc., and Spimaco.

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