



2016

CAN-BIND Depression Highlights:

A Lived Experience Perspective

The Annual Joint Workshop of the Ontario Brain Institute in conjunction with the Canadian Biomarker Integration Network in Depression, January 2016

CAN-BIND

CAN-BIND is an Integrated Discovery Program carried out in partnership with the Ontario Brain Institute

ONTARIO BRAIN INSTITUTE INSTITUT ONTARIEN DU CERVEAU

Table of Contents

Introduction

This newsletter features key highlights from the 2016 Annual Workshop of the CAN-BIND depression research program, one of the five Integrated Discovery Programs of the Ontario Brain Institute (OBI). The workshop brings together all of the researchers, stakeholders, and collaborators, to present program updates to the advisory committees, as well as to the OBI itself. The reports in this newsletter are written by members of our CAN-BIND Patient & Family Advisory Committee (PFAC), and are only minimally edited by Dr. Sagar Parikh and Adam Kagan to maintain the lived experience perspective. The PFAC is primarily constituted by members of the Mood Disorders Association of Ontario, which is CAN-BIND's partner.

CAN-BIND

The CAN-BIND Program aims to take the guess work out of psychiatric treatment for depression, by finding clear and objective ways of matching the right treatment to the right patient for various types of depression. See www.canbind.ca for more.

Reaching Out to the First Nations

A Project Proposal on Youth Suicide

Report By: **Michael Lloyd**
Based On Talk By: **Gerald McKinley & Trehani Fonseka**

Among the challenges posed by mood disorders, suicide remains pre-eminent. Within some populations, such as Aboriginal youth in Canada, suicide is an even more urgent issue, one that CAN-BIND is beginning to approach. First Nation youth are five to seven times more likely to commit suicide than non-Aboriginal youth. Youth under age 25 make up approximately 55% of the Aboriginal population, and one third of their deaths can be attributed to suicide. Risk factors include parental neglect, low self-esteem, mental Illness, substance abuse, domestic violence, history of abuse, parental loss, assault or incarceration, poor school attendance and forced to conform to other segments of society.

CAN-BIND has learned that work with the Aboriginal population requires development of deep links prior to initiation of specific projects. New ties have been established between the Arthur Sommer Rotenberg Chair in Suicide & Depression Studies, at St. Michaels Hospital and researchers experienced in Aboriginal health. Dr Gerald McKinley, a medical anthropologist at Western University and experienced researcher with First Nations, described a project being explored to increase awareness of symptoms of depression and available resources, increase ability within the community to recover more quickly, and ultimately decrease suicide rates and risk factors for suicide. The first phase will be to get input from the First Nations youth, the community Health Director, the Band Manager and with the Chief and Council to determine the needs of the community. The next phases will be to do community presentations, training for community members, educational materials, social supports and giving youths the ability to express themselves or express their points of view through photography (PhotoVoice). Ultimately, the project will provide important information to predict or prevent youth suicides in First Nations communities, and to researchers on how best to partner with those communities.

Mobile Technology and Applications to Health

Report By: **Evardina McAteer**
Based On Talk By: **Claudio Soares, Mark Matthews, Ellen Frank, Anthony Nazarov and Erica Tatham**

The CAN-BIND workshop featured a major symposium on Mobile Health, involving presentations from academic and business experts. Mobile Health (M-Health) involves the use of mobile technologies to support the delivery of health services. Most of us have watched TV commercials for devices that will automatically call for help if the wearer falls. We are already familiar with home panic buttons, baby monitors, Internet nanny-cams, and alarm systems that talk to us. M-Health is just an obvious extension of this kind of technology, into medical practice.

The principal tool in M-Health today is the smart phone. Smart phones are already in use, reminding diabetics to take their insulin, reminding patients of appointments, and performing other low level tasks. While mobile devices can be useful in physical medicine, they may be even more useful in mental health work and psychiatry.

A smart phone can have access to GPS, Wi-Fi, accelerometers, inclinometers, barometers, thermometers, proximity sensors, and many other devices that can be harnessed by an application to monitor a patient's physical situation. With these devices they can track a patient's activity levels, physical mobility, location, social interaction rates, their spending habits, and anything else that might be used to predict problems.

Mobile technologies are already being used to augment medical care by providing increased accessibility to health support and information. Patients who were initially reluctant to allow this kind of monitoring have come to like it, because they are the first to benefit from it. The benefits have been clear enough and immediate enough, that some patients have commented that they have come to think of their smart phone as a friend and companion.

For researchers and clinicians, M-Health offers the potential of providing remotely-sensed patient-centered data collection which is more complete and accurate than traditional data collection methods such as patient reported data with all its human failings. The future practicable use of mobile technologies in delivering mental health treatment is limited only by our imagination and our ability to develop effective and relevant applications.

Biomarkers and the Future of Psychiatric Diagnosis

A Critical Link to Treatment Success

Report By: **Kathryn Schade**
Based On Talk By: **David Kupfer**

Dr. David Kupfer, Distinguished Professor Emeritus of Psychiatry at the University of Pittsburgh School of Medicine, delivered the conference plenary address, "Biomarkers and the Future of Psychiatric Diagnosis: A Critical Link to Treatment Success." Dr. Kupfer recently served as chair of the American Psychiatric Association Task Force which developed the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), the handbook used by clinicians in North America as the authoritative guide for the classification and diagnosis of mental disorders. He noted that the CAN-BIND Study is the envy of researchers in the United States and offers an unprecedented opportunity for collaboration and the identification of biological and genetic markers to guide diagnosis and the development of more effective treatments for mood disorders.

While the relationship of diagnosis to treatment outcome is not a new idea, Dr. Kupfer stated that the time has come to "say farewell" to the current single category approach to diagnosis, in which all depression is seen as the same disorder, and move toward a more nuanced dimensional diagnostic system which incorporates sub-types of depression, symptom severity, demographic characteristics, medical comorbidities, and other information. Current treatments often fail, in part, because depression is a single broad diagnostic category without treatments sufficiently tailored to specific expressions of the illness. A better approach is to develop more precise interventions targeted at sub-groups of patients, such as those with melancholic, atypical, psychotic, treatment-resistant, and bipolar depression. The identification of biomarkers that provide precise diagnoses and predict treatment response is key to this process. Factors such as the timing of the intervention also merit investigation. For example, are some treatments more effective early in the course of the illness? Dr. Kupfer also emphasized the need to study variation in disease trajectories by gender, age, culture, and ethnicity and underscored the importance of increasing the participation of ethno cultural minorities in research studies such as CAN-BIND.

A Look at How to Handle a Tsunami of Data

The Emerging Field of Data Science and Integration

Report By: **Katherine Thompson**
Based On Talk By: **Ken Evans**

The CAN-BIND program collects a vast amount of data of many types—clinical information, findings from blood tests that includes thousands of proteins, genetic markers, and other biological tests, EEG, and neuroimaging. Dr. Ken Evans, in his presentation, identified the roadmap for how CAN-BIND will handle all this information. How to analyze and link all this data is itself a new challenge for the entire research community, a challenge that the CAN-BIND data science team is meeting by planning and implementing a comprehensive analytics strategy. The clinical, imaging, and molecular data from the CAN-BIND studies get put into one place, a database known as "Brain-CODE". Having all these different types of data from the CAN-BIND projects stored in a common database gives CAN-BIND researchers the ability to do integrative data analysis. While this may seem simple, it is actually creates very complex issues for the data science team to puzzle through in order to ensure quality results. There are many challenges to be addressed with such a vast amount of different types of data coming from a number of sources. Thorough data management and a comprehensive integrative analytics strategy is key. The effort required to clean the data and create and keep a tidy dataset is estimated to be 80% of the work.

Three components of the data structure that makes up the "informatics ecosystem" involving Brain-CODE: resources, software and tools for data management. In turn, there are five key components: data capture, data storage, federation, data integration and data analysis. In order to handle this, the right experts must be brought together, which the team is calling the Data Science Commons. This brings together multiple experts and analysis resources to aggregate expertise, pool resources, share tools, workspaces and integrate processes and project management. Finally, large organizations with specific expertise in different types of data must be brought together, in a forum termed the Developer Commons – Consortium. This group is led by Indoc Research, which provides molecular and clinical data management, with other organizations including the High Performance Computing Virtual Laboratory (HPCVL), providing security, large scale data storage and high performance computing; the Rotman Research Institute, providing the neuroimaging informatics infrastructure; and the Electronic Health Information Laboratory, providing data privacy and security.

Although still in the early stages, considerable progress has been made. The CAN-BIND Data Science work contributes to research, health and the economy by offering pragmatic solutions for making data science tools, resources and expertise available to the broader research community. Furthermore, it is creating avenues to extract maximum value from the data generated and providing training and practical experience for the next generation of data scientists and informaticians.

And Just What is Reverse Translation in Research?

Report By: **Darija Massey**
Based On Talk By: **Jane Foster, Francesco Leri, Pierre Blier, Xiao-Yan Wen, Cheryl McCormick**

As a new member of the Patient and Family Advisory Committee, I had the great privilege of attending the two day CAN-BIND workshop to increase my awareness about the scope of the project and my role. I was especially interested to learn about reverse translation and the role of Zebra Fish in major depressive disorder research. Simply put, how this works is researchers take scientific information from patients who are participating in the clinical study and "reverse translate" it in the zebra fish to help inform continuous improvement in treatment. One way to do science is to make observations in animals, then apply what is learned to humans. Another way is to take information from human experiences about which treatments work, and then see if a deeper understanding of how it works can be identified by using animal models.

How do animal models work? Usually some behavior in animals can be understood to represent something similar to depression in humans. Next, the changes in the brains of animals with “depression” can be identified, and then treatments can be given to the animal to see both what works to improve the depression, and how it works. Some animal models are better to understand what depression is; other models are better ways to see how medications or other treatments change the brain of the animal.

Why Zebra Fish? They grow quickly, and so brain development is quick to see and easy to study in a lab. As well, they have all the analogous parts to higher animals that can be used to understand how treatment might affect humans, both in terms of effects and side effects. A key advantage of Zebra Fish involves the fact that they are transparent, and various imaging and labelling techniques to identify various molecules can be done very easily.

CAN-BIND Data Rapid Reports – General Overview

Report By: **Janine Rosart**
Based On Talk By: **CAN-BIND Investigators**

As part of the overall workshop, there were many brief reports to give the team an update on various aspects of multiple research projects. In just 5 – minute reports, CAN-BIND investigators discussed the CAN-BIND data for Phase 1. Specifically, what the enrolled patient cohort looks like to date (1), the data platform Brain Code and making it shareable across sites (2), working with the blood samples (3) and using support vector machines for analysis (4). The last two rapid reports were of specific research studies using data (not from the CAN-BIND study) but data collected elsewhere. These studies are indicative of what types of research can be done with CAN-BIND data.

BRIEF HIGHLIGHTS FROM EACH DATA RAPID REPORT

The first patient group (Cohort 1 June 2013 – March 2015)

Dr Ray Lam provided a summary of the first group of research subjects, including 85 persons with depression and 49 controls. Both patients and controls were described in terms of age, gender, and basic clinical findings at the start of the study. Some highlights included: (a) half of the patients had physical disorder in addition to mood disorder. (b) many people had chronic disorders (c) 71% of the patients in this trial had tried at least one antidepressant. Also, some of the challenges to recruitment were discussed, including the fact that many patients see the study as too time consuming, so they decline to sign up. Those that are participating do so for varied personal reasons such as being a part of cutting edge treatment.

Overview of Brain Code *Stephen Arnott & Mojdeh Zamyadi*

Brain Code is the platform that houses all the data collected for CAN-BIND. The speakers described the 8 steps to make sure that the database can be shared across sites.

i) name checker – important to cross reference with other data
ii) scan protocol checker – checks the MRI scans, parameter values
iii) manual QC notifier – MRI quality control manual examined by eye – to ensure no obvious errors or artifacts
iv) fBIRN pipelines: phantom QA vs human QC – on a monthly basis scan phantoms to make sure things are working well
v) create data release structure
vi) raw data upload – a lot of details need to be addressed so that data can be shared – including common consent forms, standardized scan names
vii) preprocessing pipelines – fMRI and EEG data needs to be standardized across sites
viii) other – includes teleconferencing, weekly meetings.

Plasma Proteomic Methods

Dr. Ken Evans provided a brief perspective on the challenges of identifying blood derived biomarkers. As blood samples and the proteins within it are relatively easily accessible finding markers within it is relatively easy and useful in terms of applicability to routine health settings in the future. To begin the search for biomarkers, CAN-BIND had negotiated with the Lundbeck company to obtain blood samples they had collected in earlier studies comparing the antidepressant duloxetine to placebo. That analysis helped CAN-BIND refine its lab techniques and also identified some biomarkers, such as a specific protein that is linked to remission on duloxetine. Building models on a single protein may not be that relevant but building models on many proteins may be more applicable.

Biomarkers, Data Analysis, and Machine Learning

Dr. Joseph Geraci described some cutting edge approaches to using advanced math to come up with new ways to analyse data. Biomarker research has many challenges, including the fact that there are so many measured markers over multiple visits. Rather than coming up with a prediction in advance, a modern way to approach complex data is to use a statistical method and a computer technique called "support vector machines" that can methodically search for unusual patterns that allow the results to be linked to treatment success or failure.

Understanding Animal Research about Pleasure / Anhedonia and Depression *Ann Marie-Levy for Dr. Francesco Leri*

In order to deepen the understanding of how treatments work, it is possible to use animal models of depression and give depressed animals various treatments, and then see what changes there are in animal behavior and brain biochemistry that goes along with response to treatment. This speaker discussed their study using rats, sweet solution, and pharmaceuticals Naltrexone and Bupropion on the hedonic response. They found that bupropion alone, or bupropion in combination with naltrexone, was linked to a key brain chemical, BDNF, which promotes brain cell growth, in the hippocampus. Increases in hippocampal improve the ability of animals to respond to pleasure; normally, in depression, there is decreased ability to respond to pleasure (known as anhedonia).

Neurophysiology – Escitalopram & Aripiprazole on the functional activity of monamines.

A final presentation looked at the molecular effects of medication on specific neurons as well as circuits within the brain. Dr. Pierre Blier, from Ottawa, described a series of lab experiments to study the effects of escitalopram, aripiprazole, and other medications on on serotonin, Dopamine and Norepinephrine. Some drugs increase serotonin transmission while at the same time decreased DA and NE. The goal was to see if some synergy can be obtained by various combinations of medication. However, in terms of effect on serotonin, combining medications did not immediately show some synergy, but each individual drug did improve serotoninergic action. This type of research can potentially show how combined treatments already being used in people might work at the cellular level, and can also generate ideas about which drugs to combine in the future to improve treatment.

New CAN-BIND Initiatives

Report By: **Lucie Langford and Crystal Terron**
Based On Talk By: **Shane McInerney, Jeff Daskalakis, Glenda MacQueen, Kate Harkness, Sakina Rizvi, Lena Quilty/Rudolf Uher, Thenille Braun Janzen, Chris Bowie**

The meeting also featured some presentations on new developments in the research program. CAN-BIND 1 was the first study, involving using antidepressants for depression for a study lasting 16 weeks. Now, there are extensions of the original study as well as new treatment studies and related research, as shown below.

CAN-BIND 1 – Long-term follow up

CAN-BIND 1 – Long-term follow up is a naturalistic study, which means that research will be conducted by observation. This is a follow-up to the initial CAN-BIND study, which was 16 weeks in length. One of the most challenging aspects of treatment for Major Depressive Disorder (MDD) is the heterogeneity of symptoms. Based on the symptoms you have, you may fall into a specific subtype of MDD. The long-term follow up study will be used to identify subtypes of Major Depressive Disorder (MDD), which can then be used to predict more accurately the types of treatment that are best for patients, depending on the clinical subtype that they experience.

Of those patients that completed the initial 16 week CAN-BIND trial, there were 4 outcomes:

1) perfect responders;
2) non-responders to week 8 and then responded with the addition of Aripiprazole medication for the remaining 8 weeks;
3) initial responders but response was not sustained;
4) no response.

The follow-up will get in touch with patients every 6 months for five years via the internet. Phone-interviews will also be conducted.

CAN-BIND 2 – CARTBIND
Canadian rTMS treatment and Biomarker Network in Depression

The CART-BIND study is taking place at the Centre for Addiction and Mental Health (CAMH) in Toronto, and at the Toronto Western Hospital, and in Vancouver. This study is using a non-invasive technique for treating depression called repetitive transcranial magnetic stimulation (rTMS). Usually treatments with rTMS take about an hour, however, there is a new method in rTMS treatment called intermittent theta burst stimulation (iTBS) that only takes about 3 minutes. Researchers have likened iTBS to taking a "coffee break" because the treatment is so short and does not have any side effects (although some report having a headache after). This study will examine the efficacy of iTBS against the efficacy of

rTMS. Biomarker data will also be collected to understand which groups of patients will respond best to this type of treatment for depression. The researchers hope to recruit 200 participants who have been diagnosed with treatment-resistant depression and all will be given active iTBS. If the shorter duration iTBS is shown to be effective, the implications are that many more patients can be treated because researchers estimate that a new patient can be seen about every 10 minutes, increasing the capacity for treatment.

CAN-BIND 3 – PROCAN

Canadian Psychiatric Risk and Outcome Study

The PROCAN study is taking place at two sites, one in Calgary and one at Sunnybrook Hospital in Toronto. This study examines adolescents/ youth, aged 14-25, who are first degree relatives of an individual with Bipolar disorder or Psychosis. First degree relatives are usually at increased risk for also developing a psychiatric disorder. Researchers will be using behavioural measurements, measurements of cognition, neuroimaging and blood samples to identify biomarkers that could help determine the risk for developing a psychiatric condition at a young age. Researchers are also examining whether a history of maltreatment could be a contributor to psychiatric risk. The PROCAN study is one year in length but researchers are hoping to do a follow-up study and continue investigations for a longer period of time. They are hoping to recruit 270 participants and at the time of the CAN-BIND annual 2016 workshop had recruited 70.

CAN-BIND 9 – RECORD

Remote COgnitive Remediation for Depression

The Remote COgnitive Remediation for Depression targets patients who are geographically remote. Web-based cognitive remediation allows them to participate in treatment that is self-directed but is done with the supervision of a clinician. Cognitive remediation is a type of therapy that requires active training to improve memory, planning, and attention. Participants are able to communicate about the cognitive remediation tasks with a therapist via an online forum. Participants receive a phone call every two weeks to ensure that the individual is still engaging with the treatment. There are three groups being studied: those who get the cognitive remediation training for 12 weeks (short term); those who do cognitive remediation training for 24 weeks (long term); and those who do not get an active treatment (sham).

This study has many positive implications. The first being that it is available to individuals in rural and remote communities who may not otherwise have access to treatment. The second is that web-based cognitive remediation training may be beneficial for certain groups of patients, who can then engage with treatment online rather than in a traditional care setting, allowing for an increase in capacity.

Acknowledgements

The CAN-BIND Patient & Family Advisory Committee includes:

Shelley Flam
Andrew Kcomt
Carolyn Kennedy
Lucie Langford
Michael Lloyd
Barbara Marwood
Darija Massey
Everdina McAteer
Linda Millar
Michelle Millar
Janine Rosart
Kathryn Schade
Crystal Terron
Katherine Thompson
Adam Kagan (coordinator)
Sagar Parikh (chair)