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Canadian Institutes of Health Research

Institute of Neurosciences, Mental Health and Addiction (INMHA)

Substance Abuse Prevention and Treatment Initiative

Workshop Report

Ottawa ON
January 21-22, 2013

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Introduction

The Canadian Institutes of Health Research (CIHR) Institute of Neurosciences, Mental Health and Addiction (INMHA) hosted its third Substance Abuse and Prevention Workshop in Ottawa on January 21 and 22, 2013.

Approximately 50 academic researchers, service providers, and representatives from government and other CIHR Institutes attended the workshop, which featured a series of presentations on research projects funded through the National Anti-Drug Strategy (NADS) and grant money from INMHA and other CIHR programs.

Additional perspectives were provided by speakers from non-profit organizations and government departments involved in research on addiction prevention and treatment. The keynote speaker, Dr. Betty Tai, director of the Center for Clinical Trials Network (CCTN) at the National Institute on Drug Abuse (NIDA), offered exceptional insights into the workings of the network and some of its many programs.

The workshop also afforded participants the opportunity to ask questions and offer comments to the presenters, as well as to break into smaller groups to identify potential key elements of a Canadian clinical trials network. The highlights of their discussions were then presented for consideration in plenary.

This report is a summary of the presentations and discussions that took place over the two-day workshop.

Reflecting Back: Achievements Over the Past Five Years

Opening Remarks

Dr. Anthony Phillips, Scientific Director of INMHA, welcomed participants to what he called a special meeting, in that it marked the end of one period of support for addiction research and what he hoped would be the beginning of another. He commented that the heterogeneity of the group in attendance was evidence that there was an urgent need for research on the treatment of addiction from a broad range of interests.

Dr. Phillips thanked the Institute's former Assistant Director, Dr. Richard Brière, for ensuring that a solid research program in this area had been supported through NADS. He noted that some outstanding and exciting research had been funded, including three major national team grants—each of which received $300,000 a year for five years—11 catalyst grants of approximately $100,000 a year, and several bridge and knowledge-synthesis grants.

Creating a national community of researchers through the annual workshops, said Dr. Phillips, had fostered a lot of good networking, good science, and good ideas. Looking to the future, he noted how impressed he was by the CCTN and how close Canada was to being able to create its own version of the network. Dr. Tai, he commented, was on hand to share her experience and offer her assistance to help guide this effort.

In closing, Dr. Phillips commented that INMHA was preparing a report on the achievements of the past five years of research and planned to launch a request for applications (RFA) in the spring. He invited people to speak out and share their ideas and, above all, to help realize the dream of improving addiction research in Canada and finding a solution to the treatment of this challenging set of diseases.

Presentations

Primary investigators (PIs) involved in six research projects funded through the CIHR/NADS initiative provided updates on their work—some of which had already been completed, and some of which was still underway. After each presentation, the floor opened to questions and comments from the plenary.

Understanding Substance Use Among Pregnant and Early Parenting Women

- **Dr. Cecilia Benoit, Professor, Centre for Addictions Research of British Columbia**

Victoria's HerWay Home (HWH) program offers counseling and drop-in services for women who are pregnant or early parenting and are negotiating substance-use, mental health concerns, and other vulnerabilities related to social determinants of health (SDHs). The community-driven program, which opened its doors in early 2013, is modeled after similar programs that provide care for disadvantaged populations. Many of the clients in HWH identify as Aboriginal, and many have disabilities and are struggling with housing and other challenges.

Developed with support from an INMHA catalyst grant and a health intervention grant from the Institute of Population and Public Health, the program involves approximately 30 agencies in Victoria that came together as a result of growing awareness that the women in this target group were falling through the cracks of available services. To address the problem, they envisioned the creation of a continuous, locally delivered harm-reduction program that integrated health and social service supports under a single roof. Identifying strategies to take action on SDHs is another critical component.

The program is shaped by input from an advisory group of women in the target audience as well as through research. Researchers have been conducting interviews with HWH health and social service providers, local pregnant and early parenting women who identify as part of the service population, and biological fathers as a way to help define the issues these groups face in their daily lives and in service provision and to develop strategies to ameliorate these challenges. Common themes from interviews include definitions of substance abuse being problematic and infused with moral

overtones, a lack of empirical information on which substances are most harmful, the need to rethink gendered parenting norms (e.g., the capability of mothers to parent and of fathers to provide support), the prevalence of discrimination, and differences in the way problematic substance use is viewed by those experiencing it and those trying to provide services. Service providers must overcome a tendency to privilege the fetus as the client and lose the mother in the process, and find ways to enact harm reduction that move beyond abstinence.

Going forward, the program will do more analyses, continue to look for ways to take action on SDHs, and continue to examine the meaning of success for both participants and providers and incorporate this feedback into the program as it unfolds. Funding is already being sought for a third and critical phase of the program: to evaluate and address housing needs for this disadvantaged population.

Key Discussion Points:

- Social workers are part of HWH, which also includes midwives, physicians, addictions counselors, and others. They are trying to deal with the dominant discourse about addiction affecting the fetus, which comes from the child welfare system, by participating in dialogue on an alternative language for problematic substance use that acknowledges the social reality these women live in. Such a definition would allow for the possibility of a child staying with the mother in light of her support system, of which the father could be part. This could be more helpful than an abstinence approach, which often leads to the removal of the child in hospital or shortly thereafter.
- The struggle in this population is that abstinence is idealized and viewed as something everyone should be striving for. There is a lack of empirical evidence, however, around which substances are most harmful.
- An effective harm-reduction approach would be an integrated model focusing not just on drug use but also on improving other important conditions in the lives of the population (e.g., housing, nutrition). Substance use is just one of many obstacles these women face; we need a model that removes some of the others and gives them more choices with regard to how they're going to parent. We need also to prioritize the target group of women's lived definitions of what

challenges are the most pressing in their families' lives, and accept that this may not fit with the emphasis on substance use that dominant discourse perpetuates.

Effectiveness of Brief Interventions as Part of the Screening Brief Intervention and Referral to Treatment (SBIRT) Model for Reducing the Non-Medical Use of Psychoactive Substances: a Systematic Review

- **Dr. Matthew Young, Canadian Centre on Substance Abuse (CCSA) and Adrienne Stevens, Ottawa Hospital Research Institute (OHRI)**

While systematic reviews have been done to assess the effectiveness of brief interventions (BIs) for alcohol, a scoping review indicated that similar efforts had not been undertaken for other illicit substances. To address this gap, a joint project, funded by an INMHA knowledge synthesis grant, was undertaken by the OHRI and CCSA that focused on studies where screening was universal and BIs were administered to a non-treatment seeking, screen-detect population as part of the SBIRT protocol.

Ninety percent of the approximately 8,800 abstracts screened initially were eliminated as irrelevant, and full texts of the remaining 900 were then reviewed for adherence to the selection criteria. Five randomized control trials (RCTs) met these criteria: three single-site, one multi-site, and one cluster.

There was a large degree of heterogeneity among the studies in terms of the drugs targeted, screening methods employed, nature of BIs administered, follow-up time points, and other factors. Due to the heterogeneity of the studies and the fact that few addressed a given outcome, the researchers conducted a narrative synthesis of the studies, rather than a meta-analysis. A lack of information about the informed consent procedures used also made assessment difficult, and it was recommended that future protocols describe these procedures in more detail.

Three studies compared BI with no BI, and two studies compared BI with provision of written information. Most outcomes were assessed by only one study and used a variety of measures. As a result, confidence in the evidence was either low or very low, and it cannot be stated at this time whether BIs as part of SBIRT are effective or not.

Lessons learned from the review included that few studies assessed BIs as part of the SBIRT model. Of the five examined, only one followed through with referral to treatment, and most did not categorize risk level. There were also discussions about the procedures used to grade the evidence and assess risk of bias. Incomplete outcome data, selective reporting, and the lack of blinding of personnel and participants were noted as issues of bias; however, it was recognized that the blinding of personnel delivering the BI was unavoidable or very difficult to overcome.

Moving forward, the research team is considering developing a methods paper to provide guidance on the reporting of future trials and insight into ways in which studies could be made more rigorous and meta-analyzable. It was noted that even agreeing on a common outcome indicator that could be measured in the same way would be helpful in better determining the efficacy of interventions. There are 16 potentially relevant trials underway at present, the results of which will be considered for inclusion in this review once they have been published.

Key Discussion Points:

- One of the ideas behind BIs is to facilitate simpler interventions that don't have to rely on complicated clinical settings but can be delivered outside of them. It was suggested that some valuable data may have been lost by not looking at studies of non-RCT approaches as well.
- The research team considered including quasi-experimental designs that they considered sufficiently robust—including non-randomized controlled studies. Those were coded, but none met the rest of the criteria for various reasons, so there is a paucity of research of any kind in this area.
- The suggestion was made that it may be worthwhile to look at the efficacy of BIs overall. The opportunistic screening selection criteria may have restricted the ability to evaluate some good studies—and separating alcohol out also diminished some of the effects, because addiction is not homogeneous.
- There is a problem with looking at only eight papers. Maybe the research team should look at other, more "messy" studies, because there is overwhelming evidence out there that BIs are effective for certain types of things, and the World Health Organization has a huge amount of information on those benefits.

- This study did not examine the efficacy of BIs among a treatment seeking population, but rather as part of an early intervention/public health approach. We cannot say at this time whether BIs as part of SBIRT are effective, because the evidence is quite weak.
- GRADE is one of best ways to focus not on what we'd like to see but what is.
- Attrition is an important factor, because coming to a doctor's office for even 15 minutes means taking half a day off work. An important question is whether BIs might be more successful if they were done in other, more practical settings.
- Beyond the efficacy of BIs, there is also the issue of the sustainability of the approach. How many of these studies evaluated an SBIRT program that was ongoing before and after the evaluation?
- While this study did not look at implementation or sustainability of BIs, it did look at the issue of fidelity, which addresses this to some degree. In a lot of these studies, the research team expected to see evaluations of ongoing SBIRT programs and were surprised to find that a lot were RCTs in which the program began when the research began and ended when the research was complete.
- The decision to do an analysis that follows this rigorous methodology makes sense, but feedback seems to indicate that the results do not fully represent all the evidence out there. It may be worthwhile to do a separate study in which some of the exclusion criteria (in particular, around opportunistic screening) were relaxed to make it possible to examine a bit more of the evidence.
- One of the reasons for including the opportunistic screening criterion was because it is hard to get results on efficacy when comparing a treatment-seeking population to a non-treatment seeking population. However, it might be possible to look at the number of studies excluded on that basis alone to see if some meta-analysis can be done on the effectiveness of BIs in general, rather than BIs as part of the SBIRT protocol. A diagram is available showing how many studies were excluded due to specific criteria because the research team wanted to be explicit about the reason for their exclusion. That might be helpful to others in interpreting the data and the generalizability of the conclusions.

Effects of Fixed or Self-Titrated Dosages of Sativex on Cannabis Users

- **Dr. Bernard Le Foll, Centre for Addiction and Mental Health (CAMH)**

Cannabis use is a major problem globally. It is the most widely used recreational drug in the world, with three to four percent of the population having tried it at least once. No pharmacological treatment has yet been approved for cannabis addiction, and the need to create one is significant. Given the efficacy of substitution therapy in reducing dependence on nicotine and opioids, a catalyst project has been funded to determine if Sativex (a drug containing the same psychoactive components as cannabis) could serve as an effective substitution therapy for cannabis. Sativex contains both cannabidiol and delta-9-THC, the latter having been shown in some previous studies to reduce withdrawal symptoms when administered orally.

After spending a year designing the study and enduring delays caused by the terms of the contract with the drug provider and a long wait for exemption, importation, and exportation permits, the one-year pilot project is slated to begin in February. Its goal will be to demonstrate the feasibility of the approach and good tolerability of the drug in cannabis-dependent subjects, and to collect data on the effects of fixed versus self-titrated dosage regimens. The primary outcome measure will be effect on withdrawal, cravings, and consumption.

The study will involve subjects who are frequent users of cannabis, who have a current cannabis dependence for which they are not seeking treatment, and for whom cannabis is their primary drug. It will take place over eight weeks: during the first four, they will be allowed to smoke as usual; during the next four, they will be asked to abstain from smoking and will, instead, be randomly selected to take either active Sativex or a placebo in either self-titrated or fixed form.

The experimental treatment for the study will be done on an out-patient basis, with patients being given a vial that is good for two days and coming in daily to have it weighed to see how much they have used. Clinical, physical, and substance-abuse assessments will be done both before, during, and after the study, with a questionnaire administered and blood and urine samples collected once a week.

Lessons learned so far include the importance of having a team with complementary expertise, resilience, and adaptability—and of striking a balance between the interests of the PI and those of industry (e.g., pharmaceutical). The research team has applied to NIDA for an RCT that it hopes to carry out in parallel with this pilot. In the NIDA trial, treatment would take place over 12 weeks—with the dosage of Sativex gradually being increased over the first two weeks and then maintained at that level through week 12, after which there would be follow-up. Going forward, it is hoped that the study's data will serve useful to larger studies and set the base for developing a novel treatment for cannabis dependence.

Cannabis Addiction and Psychosis: A Preclinical Model

- **Dr. Pierre-Paul Rompré, Professor, Department of Psychiatry, Université de Montréal**

For people diagnosed with schizophrenia, the prevalence of substance use is almost 50 percent—and the illicit drug they most consume is cannabis. Cannabis addiction has a significant detrimental impact on these individuals, many of whom are younger. They more frequently experience worsening of their symptoms, are less compliant in using their medication, and relapse more often, resulting in more frequent hospitalizations. Their prognosis is much worse than for those who do not consume drugs.

Most of the basic research aimed at understanding the effect of cannabis on behaviors and the modulation of limbic brain functions by endocannabinoids has been carried out on normal animals. To help determine why cannabis consumption is higher among schizophrenics and test the theory that it may be more rewarding or less aversive to this population, a study was launched under an INMHA catalyst grant to to investigate the role of tetrahydrocannabinol (THC) and a cannabinoid agonist (CA) on different reward-relevant behaviours.

The study was aimed at developing and validating an animal model of this co-morbidity; identifying neurobiological abnormalities that led, in the model, to abnormal responses to cannabinoids; and identifying the mechanisms by which the neurobiological abnormalities arose. To achieve this, an animal model of psychosis was used in which baby mice underwent a bilateral lesion of their central hippocampus. This resulted in symptoms analogous to those observed in psychotic patients when the

mice were adults. The animals were then used to study the effects of D-^{9}THC and WIN 55,512-2 (a CA) on three reward-relevant behaviors: forward locomotion; rewarding electrical brain stimulation, and conditioned place-preference.

As expected, amphetamines induced a larger increase in forward locomotion in lesioned than sham animals; however, this was not observed at an early age. The reward-enhancing effect of amphetamines did not differ between lesioned and sham adults but did between these same groups of young animals. A low dose of D-^{9}THC induced a transient conditioned aversive effect in adult lesioned animals but not in young lesioned animals and a weak attenuation of reward in sham animals but not in lesioned ones. At a low dose, WIN 55,512-2 tended to increase forward locomotion in lesioned adult animals but not in sham ones, an effect that was age-dependent. At a high dose, the CA produced a strong attenuation of reward in adult lesioned animals but not in sham ones; however, these results must be confirmed with a larger sample. Adult lesioned animals also had a lower level of CB1 receptors in the ventral striatum compared to sham animals.

These findings reinforce the relevance of investigating behavioral effects of drugs using animal models of psychiatric disease. A big challenge is the need to improve the model by introducing antipsychotic treatments and chronic drug exposure to better mimic the clinical situation. Age is an important variable as is differences in behavioural assays. Next steps will be to complete dose-response studies of D^{9}-THC, agonists, and antagonists; map the distribution of the enzymes monoacylglycerol lipase and fatty acid amid hydrolase mRNA; and investigate the endocannabinoid modulation of GABA and glutamate neurotransmission using *in vitro* electrophysiology.

Key Discussion Points:

- A protocol in which the animal took the cannabinoid chronically (e.g., self-administered from an early age) would be more translatable.
- Data show that cannabis consumption prior to age 15 has increased—with addiction increasing but not psychosis. It would be valuable to see if studying this in a lesioned animal might make it possible to predict whether withdrawing the drug increased the cognitive deficits further along.

- The comorbidity of cannabis use and mental health is an important area. A recent study on the subject found that 85 percent of cannabis is smoked by people with mental illness. The questions around that are not just the effects of THC but also what cannabidiol may be doing in the equation?
- There have been some interesting findings around cannabidiol, which would likely oppose the effects of THC. It has been found to block cocaine reward; in another study, they found that those who consumed a plant that had a low level of cannabidiol had more chance of developing psychosis than those who didn't; cannabidiol has also been developed as a possible antipsychotic treatment. It would be more ecological to study cannabis and cannabidiol chronically.
- Would the normalization of prepulse inhibition be a strong marker for the antipsychotic effects of a drug, and are there plans to incorporate that into this methodology?
- It would be interesting to see if WIN had an anti-psychotic effect, but the modulation of cannabinoid is extremely complex and could go in both directions. It is a complex system.
- Studies of the effect of ventral hippocampal lesions have shown that the acquisition of sucrose and cocaine through self-administration is faster and the rate is higher; however, this hasn't been done for amphetamines. Macrodialysis studies suggest that the differences may be post-synaptic. If you use a different reward paradigm, you can get different profile: the effects are not just interchangeable.

Non-Medical Use of Prescription Opioids in Canada: Epidemiology, Consequences, and Interventions for Public Health

- **Dr. Benedikt Fischer, Simon Fraser University, Centre for Applied Research in Addictions and Mental Health**

According to US data, non-medical prescription opioid (PO) use is on the rise in the general population, and street drug-user populations have made a significant shift from mainly heroin to POs. This has caused a significant increase in PO-related morbidity and mortality, with 15,000 people a year in the US dying as a result—out-measuring deaths from heroin and cocaine overdoses put together.

Canada and US are world leaders in overall PO consumption, but there is a lack of Canadian data on morbidity, mortality, or treatment. To address this, a national research project was launched to assess the epidemiology of non-medical use of POs in general and special populations; assess key determinants and the extent of opioid-related harm, including morbidity, mortality, and the burden of disease; develop and assess key interventions (prevention/treatment/policy); and undertake knowledge translation.

An examination of available epidemiological data found the rate of non-medical PO use in Canada relatively low (0.5 percent of population); however, a closer look found this rate was due to initial surveys characterizing non-medical use only for the purpose of intoxication. Depending on how the question was phrased, the rate was four times higher—indicating that a large "grey area" exists between real abuse and intoxicating use and other forms of use with self-medicating purposes.

A recent paper from the Centre for Addiction and Mental Health showed the level of non-medical PO use among adults in Ontario at about six percent and 15.5 percent in the high school population. Unlike other psychoactive drugs, which are more popular in quasi-marginalized populations, PO use is prevalent in most social demographics and economic groups—indicating that it needs to be tackled more broadly than some other substance-abuse problems.

A comprehensive literature review found comorbidities with mental health and pain disproportionately high in non-medical PO users—not surprising, as POs are also used in the treatment of these conditions. A sub-study on provincial dispensing patterns found that dispensing was increasing in all provinces over time, with major quantitative and qualitative differences among provinces. A possible factor behind higher rates in Ontario and Alberta may be the absence of prescription monitoring, as both Quebec and BC have lower rates and electronic monitoring systems in place.

In Ontario, from 2004 to 2009, there was a substantial increase in the number of people presenting to addiction programs with PO-related problems or dependence. A comparison of per capita use and per capita treatment in the province found an almost perfect correlation. A similar correlation has been found between accidental overdose-

related deaths from POs and the quantity of POs dispensed. While this points to a need for greater policy controls, a significant challenge is that POs are needed by people with severe and chronic pain.

Oxycontin has now been delisted in several provinces; however, substitution effects and other impacts have not yet been examined. Needs going forward include the evaluation of such policy changes and treatment interventions, better and more systematic national and comparable data, and ongoing monitoring and studies.

Key Discussion Points:

- There are a lot of other factors that allow people to get into trouble using these drugs (e.g., hyperalgesia, different pain thresholds, higher level of personality disorders, more sensitivity), so there is a need to focus more on the individuals who have problems with POs than just on the medications themselves.
- There have to be much more responsible ways of dispensing. Both the providers and the system itself are problems. Canada dispenses five times more POs than the UK or most western European countries, but we don't have more pain in our population. So changes have to happen there as well.
- One group that gets missed in all of this is the manufacturers and pharmaceutical companies that have products to sell. Where is the vector control in this? That is absolutely part of the system and needs to be addressed.

The Genetics of Drug Dependence: Mapping Genes for Cocaine-Related Behaviours in a Mouse Model

- **Dr. Kathryn Gill, McGill University Health Centre**

Little is known about why certain individuals progress from drug taking to drug abuse; however, twin studies have provided considerable support for the heritability of cocaine addiction. Hoping to someday have a gene that is targetable in a therapeutic sense that could be used for the treatment of cocaine addiction, researchers funded through a bridge grant are conducting animal studies to map genes for cocaine-related behaviours.

Mice are genetically well characterized, and a large number of genetically diverse inbred and recombinant inbred mouse strains are commercially available. Rapid breeding turnover makes it possible to examine genetic correlations across multiple behavioural, biochemical, anatomical, and neurochemical phenotypes. Various inbred mouse strains show different susceptibility to human diseases (e.g., colon cancer, obesity) and heritable differences in their responses to drugs of abuse.

Looking at a number of potential candidate genes that have been replicated in multiple different strains, researchers found four promising genomic regions containing genes that were expressed in the brain, with functional effects on proteins of interest. Genetic mapping studies using recombinant strains of mice confirmed a locus on mouse chromosome 18 that accounted for a large proportion of the variance in response to the psycho-stimulant effects of cocaine.

A strong candidate gene, the deleted in colorectal cancer gene (Dcc), was identified using *in silico* bioinformatic techniques. Dcc is a netrin receptor (netrins guide cell and axon migration during brain development) and it is involved in the organization of the dopaminergic system. Prior research demonstrated that Dcc null mutants show a blunted behavioural response to amphetamines. A Dcc knockout (KO) mouse was obtained from a collaborator at the Montreal Neurological Institute.

To test locomotor activity, the Dcc KO mice received intraperitoneal injections of saline on days 1 and 2, followed by injections of cocaine (5 – 40 mg/kg) on day 3. Results showed that Dcc heterogeneous (Dcc het) mice were significantly less sensitive to the behavioural activating effects of cocaine. Tests involving intravenous self-administration (IVSA), in which the mice were trained to press a lever to receive injections of cocaine, saw a ceiling effect, with the Dcc het mice quickly hitting the maximum number of injections available. Dcc het mice showed higher drug-seeking behaviour as measured by higher breakpoints under a progressive-ratio schedule of reinforcement (some hit up to 300 times for a single injection of cocaine). There was no difference between genotypes under a fixed ratio-schedule of reinforcement (there is a need to test higher response requirements).

The Dcc KO has the mutation present during development, which could lead to interactions with other brain systems. Moving forward, researchers plan to examine

cocaine IVSA in a conditional Dcc KO in order to disentangle the developmental and regulatory alterations from the acute effects of the gene. The Dcc KO will be specific to mesolimbic dopaminergic neurons in the brain (starting at day 16 of development) using a Cre/LoxP targetting strategy. A key focus will be to examine the Dcc gene and protein expression studies in naïve and cocaine-exposed animals. This work will begin shortly, as the mice of interest and control mice will be ready by the end of February.

Key Discussion Points:

- This is just one example of how animal models make a good companion piece to some human genetics studies and that collaborations and exchanges of information between the two should be more frequent.
- It is predicted that Dcc mice would exhibit differences in preference for or reactivity to many other drugs of abuse. There is no difference in terms of ability to learn or in consumption of sweetened milk, however, so for basic sucrose-related rewards there would not likely be any difference. There is a strong signal on chromosome 15 that maps to alcohol, cocaine, and nicotine. If there is a chance to do more work in this area, it would be interesting to see the common elements that regulate those three drugs of abuse.
- The behaviour profiles of Dcc KO mice are fairly normal. With the conditional Dcc KO, however, we will be affecting the overall development of dopamine, so there may be a fair number of effects.
- If we want to determine whether the gene is affecting aspects of cocaine reward or knocking out satiety—we have to design studies to determine that. If you give any animal model unlimited access to IV cocaine, they overdose very rapidly, and they are too important to allow to go all the way.
- The progressive ratio procedure you use where animals can press 300 times to get one injection is commonly thought of as a test of motivation. So it may be that you're affecting motivation and willingness to work. Satiation is a good point, but tests are needed to also determine if this is compulsive behaviour.
- Students talk about the mice getting their teeth on the lever and pushing it until they run out of cocaine—then they go to the inactive lever. So there is high motivation for the cocaine; also, they get driven because they have so much cocaine in them. So it is difficult to interpret.

- In rats and monkeys they do second-order conditioning, where they press 15 minutes only for light, then get a drug reward. So there are ways of dissecting out intense motor activities.
- Going back to early work and the whole question of whether animals show similar extinction patterns, the progressive ratio break-point data are very impressive, but in particular circumstances, would they show natural extinction patterns?
- When we have done progressive ratios, we have done them for two days and then stopped. We would have to run them longer and see if the inactive lever is extinguished and then see how quickly it is reinstated. This work is focused more on gene mapping.
- In rat literature right now, it is pretty much established that if you have a combination of three criteria—that they will continue to look for the drug even if it is not available, there is punishment, and there are progressive ratios—that is addiction. Only 20 percent of rats will meet those three criteria; the work has not yet been extended to mice.
- Cre Lox is an excellent tool that can knock out very selectively in different tissues.

Keynote Presentation

Clinical Trials Network: Recent Trials and Future Directions

- **Dr. Betty Tai, Director, Center for the Clinical Trials Network (CCTN), National Institute on Drug Abuse (NIDA)**

NIDA's Center for the Clinical Trials Network (CTN) was established in 1999 with the bold mission of improving drug abuse treatment in the US using science as the vehicle. The network brings together substance-use disorder (SUD) treatment researchers and providers to foster bi-directional communication and ensure that trials conducted are relevant to practice. Specifically, the network conducts rigorous, multi-site effectiveness trials in real-life community settings and transfers results to clinicians, providers, and patients. Asking research questions that, once answered, will impact practice and balancing external and internal validity are paramount. Since its inception in 1999, the CTN has developed 52 clinical protocols, enrolled 15,000 patients in 36 clinical studies, and completed 28 trials of behavioural therapies, pharmacotherapies, and integrated

treatment strategies—26 of which have published primary results. Currently composed of 13 Regional Research Training Centers, 57 university affiliates, and 240 community-based treatment clinics, it works closely on research translation and dissemination in collaboration with its sister organization, the Substance Abuse Mental Health Service Administration via its Addiction Technology Transfer Centers.

Some examples of the many trials in which the CTN has been and is currently involved include the following:

- *Prescription Opioid Addiction Treatment Studies:* Adding enhanced medical management to a treatment regime of buprenorphine/naloxone and drug counselling did not affect improved treatment outcomes for people with PO addiction, who experienced nearly universal relapse with only detox management.
- *HIV Rapid Testing:* Offering patients the opportunity for a rapid HIV testing kit on-site when they entered into drug addiction treatment resulted in 82 percent of people being tested and receiving test results, as opposed to 14 percent of those who were referred out for off-site testing. A brief risk-reduction intervention administered at the same time as on-site testing had no effect on the reduction of risk behaviour.
- *Web Delivery of Evidence-Based Treatment*: Using an interactive web-delivered therapeutic education system (TES) to teach patients various skills was no less effective than having the usual treatment delivered by a counsellor.
- *Smoking Cessation and Stimulant Treatment*: Results have not yet been published of this evaluation on the impact of concurrent outpatient smoking cessation and stimulant treatment on stimulant-dependence outcomes.
- *Cocaine Use Reduction with Buprenorphine*: Enrollment has been completed for this study, which will test claims that buprenorphine could be used as a treatment for cocaine dependence.
- *Buspirone for Relapse Prevention in Adults with Cocaine Dependence*: Unpublished data suggests that buspirone may be effective in relapse-prevention for recently abstinent cocaine-dependent patients. The first stage of the two-part study is a safety evaluation that has, so far, shown good tolerance of the drug by patients.

- *Screening, Motivational Assessment, Referral and Treatment in Emergency Departments:* Results of this study, which aims to contrast substance use and related outcomes among substance abusing emergency department patients randomly assigned to one of three different treatment situations, are under analysis. Treatment exposure was robust, with overall retention being 85 percent at three months.
- *Manage Substance Use Disorder with Chronic Care Model*: The CTN was invited to join this study funded out of the US Center for Medicare and Medicaid and led by Duke University, which is intended to improve diabetes patient management in safety net primary care settings, to determine whether doing a drug SBIRT at the same time would improve both diabetes and SUD.

Several new changes under US health care reform (Affordable Care Act, 2010) will greatly affect drug-abuse treatment in a very positive way. One is the requirement that all health plans are, by 2014, to offer prevention, early intervention, and treatment for the full spectrum of SUDs, with reimbursement to be no less than that for any surgery or disease treatment. Another is legislation around Health Information Technology for Economic and Clinical Health (HITECH Act, 2008), which defines the certified and meaningful use of electronic health records (EHRs) and not only provides incentives for adoption but also requires all EHRs to be digitized by 2017 by major providers in order to continue to receive reimbursement.

The new Patient Centered Medical Home (PCMH) chronic care model for SUDs offers a full spectrum of services for SUDs, including a single treatment plan for both medical and behavioural components, and takes a team approach to care delivery. This model is an opportunity for prevention efforts to change the lives and habits of the some 60 million Americans classified as "unhealthy or harmful users" before they hit rock bottom. It also provides incentives to big pharmaceutical companies to find ways to treat this large demographic.

The CTN plans to propose a well-designed, large-scale, multi-site trial to determine how to effectively implement SBIRT for SUD in primary care. The network is also developing common data elements (CDEs) for SUDs to be used by researchers and providers in capturing research and patient-care data. One example is the development

of CDEs for a single-question screener, followed by the DAST-10 assessment tool, to enable primary care physicians to screen and assess for the risk and severity of drug use and make an informed decision to either deliver a BI on the spot or refer the patient for specialty treatment based on their assessment. The CDEs will also simplify the future merging of research data and EHRs.

The overarching message was that more clinical trials were needed to assess the effectiveness of interventions in improving the prevention and treatment of SUDs.

Key Discussion Points:

- INMHA has a number of travel awards available for researchers interested in attending this year's CTN meeting, which will take place in Washington from March 13 to 15. More information is available on the Institute's website.
- With regard to the detoxification study on opioids, we are still focusing too much on the drug and not enough on the drivers and determinants around this issue. When we go back to the powerful and potent issue of comorbidities, chronic pain and chronic mental health are drivers of this kind of non-medical use. If they are not addressed, people will relapse.
- Well powered, large multi-site trials are the gold standard for developing and informing more effective ways to deliver evidence-based medicine. Large pragmatic trials are for the benefit of providing external validity that small, well-controlled study failed to accomplish.
- The CTN is funded through a cooperative agreement mechanism under which the federal government and grantees work together. Funding is provided to the universities, who subcontract to the treatment providers. A steering committee made up of researchers and providers serves as the governing body for major decision-making regarding the research and administrative issues related to the network. Communication is key, and there is lots of give and take. In terms of sustainability of the evidence generated by the network research, the community providers do the research—so they create a "learning healthcare system".
- Large-scale trials are needed for comparative effectiveness research, but this does not suggest that smaller-scaled efficacy studies should be ignored. Certain trials, especially for medication, may have to employ a phased approach.

- The CTN's work, so far, involves trials of few experimental medications, as the network is not intended for the development of medication but to focus on comparative effectiveness and implementation trials.
- New research ideas come from the granted investigators: that is the NIH cooperative agreement grant policy. The research concepts generation process in the CTN is such that, whether the investigators are providers or researchers, they approach the CTN with their research concepts. From there, we sit down, brainstorm, select the most meritorious concepts and go from there. Ideas bubble up from the community through the connection they have with an investigator. The investigator then submits those concepts for consideration through the CTN's Research Development Committee.
- In Canada, we are starting to realize that the primary care setting is not necessarily the only one in which to deliver prevention or most interventions for young people—as they are generally healthy and are not often seen in that setting. So other strategies are needed.
- Our network works mostly with providers on clinical trials, but NIDA has a prevention research branch that has some school-based programs. NIDA also has a grant portfolio for SBIRT for primary care and adolescent care. For adolescents, the screening tool is different than for adults, and supplements are currently being provided for the development of potential new tools for this group. Two child psychiatrists are submitting a joint proposal for a CTN research concept to do a SBIRT for adolescents in primary care settings.
- In terms of how the CTN manages local reviews from each Institutional Review Board (IRB) at each research site for multi-site trials, the network has, at times, used commercial IRBs because they are faster. An important aspect is fostering good relationships; early on, CTN researchers formed joint teams to make presentations to local IRBs to familiarize them with the special needs of SUD patients and trials.
- Maintaining adaptability in studies is very difficult; it all comes down to paying special attention to selecting good study concepts, having a good design, and having a user-friendly implementation strategy.
- Cluster randomization may be an effective way to do comparative effectiveness studies, but it requires a large number of patients, so there are trade-offs.

- The CTN provides a centralized resource, the Clinical Coordinating Center, and the clinical data management and statistical center to support the development of protocols (and methodology), data collection, statistical design, training, data monitoring etc. At the same time, many design ideas come from investigators.
- In setting up a new network, it is important to create a flexible infrastructure, because research directions and needs will change. The ability to accommodate urgent public health needs and unique scientific opportunities will dictate the kind of network needed. Infrastructure dollars should be kept relatively small to leave more money for research. Rather than provide funding in one installment, it would be ideal to provide reimbursement based on per randomization. Recruitment dictates the cost of trials, because the longer it takes, the more it costs. Sometimes a rigid protocol is a stumbling block, so it is important to make that as general as possible and put more specifics in the operational menu. It is easier and faster to modify the protocol to improve performance; otherwise, each protocol amendment will have to go through the IRBs, in most cases.

Looking Forward: The Next Five Years

Presentations

Presenters on the second day of the workshop provided a slightly different perspective on addiction treatment and research, not only representing both government and non-profit programs but also work focused on special populations—including immigrants, youth, and First Nations and Inuit people.

Non-Profit Reality

- **Richard Dubras, Executive Director, Richmond Addiction Services**

Richmond, BC, is a culturally diverse municipality—with 89 different first languages listed in the 2011 Census. In 2006, 65 percent of the population was a visible minority: the second highest proportion of any municipality in Canada. A first home to many new immigrants, Richmond also has the highest proportion of Chinese residents in the country by a wide margin and a large number of people from South Asia. This presents a number of linguistic, cultural, and ethical challenges to substance-abuse treatment, one example being the very negative connotation the word "addiction" has in Chinese.

Richmond Addiction Services makes ongoing attempts to remove these barriers, ensuring that some staff members are multi-lingual, offering education to clients in their native language, where possible, and even training elders to go back into the community and connect its members with resources. The agency provides school- and community-based programs as well as special programs for older adults, youth, and families—all funded primarily by the local health authority and grant money from the City of Richmond grants process. Most funding goes toward salaries, so finding room in the agency's small program budget for evaluation and measurement is a challenge.

Recognizing the need to assess its impact, however, the agency supports as much academic research as possible, contributes to community environmental scans, and fosters relationships with universities. It recently evaluated its Peer 2 Peer Program by working with the Canadian Centre for Substance Abuse to assess the impacts of the school-based Program. Limited resources for data analysis and a lack of statisticians on

staff, however, greatly impede its abilities as funding and contracts are tied very closely to direct client service. Richmond Addiction Services does annually evaluations of the Constructive Alternative to Teen Suspension Program through pre- and post-testing, as well as by comparing results to a control group.

To connect with a research group or create linkages to work being done by the research community would be of great benefit to the agency, which places emphasis on working with non-profits to develop funds and improving access to ethnic groups through pilot programming and the integration of research findings into practice. The chance to make an even bigger difference lies in secondary prevention and taking the opportunity, when dealing with other health issues (e.g., diabetes) to check for concurrent ones, so people are made aware of areas of overlap.

Key Discussion Points:

- Most organizations don't conduct evaluations, except process evaluations. We need to see the culture change and people at the executive-director level who have more sense of the time, resources, and expertise it takes to evaluate. There has to be support for leaders to collect the data and ask the questions.
- The problem is that most funders don't know what to expect in terms of outcomes, so service providers are hesitant to demonstrate effects that might seem too low (even a 20-percent long-term success rate is high). There needs to be information-sharing and education around standards, expectations, and how to work together to connect research to what is really happening.
- Other non-profits have the same concerns: all are given money to provide a service, not to conduct evaluations, yet funders want numbers to justify their investment.
- The way the granting process takes place doesn't allow for long-term follow up and evaluation, because there isn't sufficient money to continue projects for that length of time. In some cases, money for evaluation has come from external sources because it is not in the mandate of the local health authority.
- If possible, it would be useful to build in a "booster session" with an evaluation component attached to it.
- This makes a good case for an integrated research network in Canada. It affords new opportunities for researchers looking for sample populations and would be

of practical use to service providers, who are informed and interested but do not have the resources for evaluation as it may not be part of their mandate. If the two groups worked together, they would benefit from expertise in research and evaluation as well as data collection in a clinical-practice setting.

The Co-Venture Trial: A Cluster-Randomised Trial Investigating the Impact of Alcohol Prevention on Cognitive Development and Addiction

- **Dr. Patricia Conrod, Associate Professor in Psychiatry, Université de Montréal**

The majority of substance-use disorders (SUDs) have first onset during adolescence. This is a significant concern because the brain undergoes important maturational changes during adolescence and adolescent-onset substance misuse heightens the possibility of addictive problems later in life. A number of studies are underway looking at SUDs in adolescents, including a US trial to determine the extent to which early alcohol exposure causes a neurotoxic process at a critical period of development.

Evidence shows that personality traits are implicated in substance use and co-occurring disorders. A European study that, among other things, is analyzing the neuro-imagery of 2,600 fourteen-year-olds, has found that activation scores in various key areas of the brain that are implicated in simple behaviors are also associated with substance-using behaviour. There is growing recognition that this interaction is quite complex, and that some brain structures and functions might be implicated in the risk for early onset and others more susceptible to early-onset drinking and degree of use. Imagery taken of the same subjects at age 18 will make it possible to detect whether those who began drinking early and heavily have different brain development than those who did not.

Efforts to more toward earlier interventions show that "indicated" interventions, such as brief motivational interventions for heavy drinkers, tend to have time-limited effects. They also show limited efficacy for universal, school-based approaches. To look at the relatively untapped area of "selective" intervention, a brief program for teens with high-risk personality profiles is being brought to scale in the United Kingdom and Canada. Evidence indicates that personality-targeted interventions delivered by teachers delay the uptake of drinking and decrease the risk of alcohol-related problems,

and that high-risk individuals who receive personality-targeted interventions also have much lower rates of cocaine use.

Results were recently announced of a UK trial looking at the effects of personality-targeted interventions on the alcohol use of high-risk children and the "herd effect" on low-risk children in the same school. Preliminary findings showed that, in schools without interventions, low-risk students caught up to high-risk students in terms of drinking prevalence and frequency, while rates were lower for both groups in schools with interventions. Furthermore, all children who received personality interventions had improved depression, anxiety, and conduct outcomes, and those categorized as "impulsive" demonstrated less bullying behavior.

Inspired by these findings, the CIHR-funded Co-Venture Trial is looking at the causal pathway of alcohol addiction from early onset of use. Randomized schools will deliver a personality-targeted program and follow high- and low-risk students over a period of five years—testing for the effects of delaying early onset substance use and misuse on cognitive development, the development of emotional and behavioural problems, academic outcomes, and long-term addiction problems. Real-time data collection using school computers will help improve access and follow up. The last component of the trial will be to add a neuroimaging component.

Key Discussion Points:

- No significant sex differences have emerged from this study yet. Gender is controlled for early on by selecting kids who are at the highest end in their school in terms of personality type and need, so the groups tend to be matched by level of impulsivity. There hasn't been any evidence of girls or boys responding differently to interventions in this study. With regard to predicting treatment outcomes, it appears the higher the level of impairment, the better the response.
- In a longitudinal study of impaired driving, female cohorts have proven much harder to recruit than males. Cross-sectional data show that women who come into view for a first-time offence show more impulsivity problems than men. In terms of becomes persistent impaired drivers, we see an interaction whereby it

becomes impulsivity in the males and more persistence of alcohol involvement in females. It is very complex.

- The key to success in having researchers from different sites work together is to create a design based on evidence and good design, more so than consensus. If you try to get consensus on a large scale, it results in compromises and washed-out effects. It is also best to enlist the expert who has the best track record with the intervention that is being tested to write the operating procedures and do the training at other sites. Holding regular workshops for RAs and evaluating how well they deliver a protocol is also useful. Ongoing monitoring is a big part.
- While Canada has sufficient scientific expertise to do multi-site studies such as these, there should be no problem with inviting experts from elsewhere to join or even lead a particular part of the study, if necessary. The funds would remain in Canada with the site or with a local PI partnered with the external expert.

First Nations and Inuit Health Branch (FNIHB) Health Programs and Data Collection Activities

- **Dr. Samir Khan, Health Canada, FNIHB**

Health Canada has attempted to collect data related to Aboriginal health and health services for many years. Over the past decade and a half, there has been a move toward a more collaborative approach to research and data collection that engages the local community in identifying knowledge gaps, reports back on results, and builds local capacity to track and use information. Establishing trust is key to these efforts, and data-sharing agreements between those involved reflect a spirit of respect and collaboration. Information is gathered on a wide range of factors (e.g., care practices, access, health status, potential risk or protective factors, implementation of clinical practice guidelines) using a variety of tools, including manually completed surveys and teleforms. Process maps are used to explain the care process and create a feedback loop as the process evolves.

While the First Nations Regional Longitudinal Health Survey (RHS) collects data on the percentage of on-reserve residents who have used a specific substance over the past year, it does not collect information specific to addictions. Health Canada is now working with the First Nations communities on a treatment outcome study that has

obtained data on the history of addiction, demographics, and treatment of 2,500 clients, which is followed up on an annual basis. It includes getting evidence-based support for outcomes of cultural treatment strategies, such as sweat lodges and healing circles. The communities have been highly engaged in the effort, including in the interpretation of results, and health workers are using the data to evaluate and modify their programs. Important research issues going forward for FNIHB include prescription drug abuse, the role of concurrent disorders, the development of culturally safe and relevant treatment options, and situating the understanding and treatment of addictions within broader mental health and/or social contexts.

Key Discussion Points:

- Caution should be used in interpreting a rise in opioid use in aboriginal communities with comorbidity factors. Those factors may have been there long before opioids flooded in, as 50% of adults had prescriptions for drugs. So there are systemic factors that need to be considered rather than simply pathologizing the populations of interest. That part of the analysis needs to be undertaken to understand how the problem arose and emerged.
- If data point to the efficacy of strengthening First Nations identity, how, at the same time will we move toward better integration (i.e., reducing unemployment) and address other issues that perpetuate some of the difficulties in these populations?
- The broader idea of integration is an extremely sensitive one to suggest to any First Nations community, as they have been here for thousands of years, have their own traditions, and question the reason for integration. As much as possible, Health Canada tries, from a narrow health-service perspective, to examine how identify is associated with healing. Identity is important because there has been a dissociation in the past and also because there is evidence of a healing effect with an improved sense of cultural identity and understanding. This can create a buffer against stresses in general: for example, it has been observed that language, if spoken by family or community members, has a connecting and protective effect. FNIHB's focus is on how to enhance this.

Breakout Session: Building a Canadian Research Network

Recognizing the need for continued research on effective interventions that addressed the complexity of addictive behavior and a formal structure to facilitate and evaluate that research, and inspired by the example set by NIDA's CCTN, INMHA proposed the creation of a new Canadian research initiative in addiction.
The Clinical Intervention Network, as it was tentatively named, would focus on substance abuse (drugs, in particular) and would be composed, initially, of three to five nodes. Having researchers and service-providers work together at these nodes would give experts in trial design access to specialized patient groups who could be engaged in the assessment of promising interventions. This would also ensure that all trials adhere to the principles of rigorous, quality-controlled clinical research.

Approximately $7 million would be made available from INMHA over five years to build the network and provide annual support for infrastructure. Trials and studies would either be funded within the annual budget or through partners. The concept was that a "bubbling up" process would be used to bring forward ideas for trials and studies. Proposals would then be submitted to a steering committee for consideration and the best ones recommended to the funding agency, whose decision would take into consideration the committee's input. Selected proposals would then be peer reviewed by external experts to evaluate their validity and methodology. This would be a much faster and more nimble process than an open competition or strategic program and would also enable the network to respond quickly to interest from other groups to fund specific studies.

Participants divided into three groups to discuss this proposal in more detail before reporting back in plenary on the outcomes of their deliberations. Up for discussion, in particular, were whether such a network would be worthwhile and specifics related to the integration of researchers and service-providers; governance principles; ethical approval for studies; methodology, training, and data analysis; data sharing; innovation versus translation; and priority studies for consideration.

Group 1:

- There is a need for an addiction-related trials network in Canada.

- This must be a broad initiative that is inclusive, takes into consideration the many voices at the table, and is attractive to a number of different stakeholders: researchers, policy-makers, health service providers, clinicians, primary care, educators, government and non-government funding agencies and decision-makers, etc.
- Results need to be translatable to a wide variety of stakeholders.
- The value proposition is critical: what is the purpose of the network?
- Priorities are important: someone has to be able to make a decision based on the list of potential projects.
- Focus is important because the funding won't go far. We need to start small with achievable goals and grow as we prove ourselves.
- Natural leaders will emerge with different strengths. They, in combination with the interests of the broader community, should help define priorities.
- Theme-based nodes would be preferable to geographically based ones.
- The network has to serve both functions: pure science (e.g., RCTs) and implementation in a natural setting.
- Building on the experience of other stakeholders and using that for leveraging purposes is important.
- The US model is a good one.
- We need to build collaboration and partnerships.
- We need to define nodes.
- Nodes should be university-based with service-provider partners and in places that have proven trial expertise.
- The network's efforts must be recognized as valuable to the general community in order to be sustainable.
- The network itself will need to be evaluated to see how it is functioning.
- We need to develop a common agenda and clarify the process.
- We should focus on this as a trials network and emphasize phase-3 trials as part of its work.
- There needs to be a conversation between service providers and government around major, emergent problems and priorities and existing research expertise.
- The possibility exists to reach out internationally, as well.

- The $7 million is essential to fund the network infrastructure, and it should not just be lost in projects. If the network succeeds, project money will be attracted by the structure that has been built.

Group 2:

- The US model has many good features and is an opportunity for collaboration.
- Should the network be built and then populated with ideas or should we create a vision of the kind of research to be done and build the network around it?
- Preoccupations might be better served by RCTs.
- Building a culture of research is an important output of this effort.
- What kind of research design is best served by a nodal structure: does it favour RCTs over other methodologies that might better answer questions pertinent to the practice milieu?
- Are we limited to clinical samples or is there room to look at selective prevention?
- Is a node geographic or it is part of a growth strategy? Does it reflect more population distribution or existing capacity, or is there a grander scheme to build capacity through the development of nodes?
- What are the terms of reference for creating the nodes and the network?
- What is the difference between the team grant structure and the concept of a network?
- What other players should be part of this process (e.g., neurophysiologists) and is the network open to considering places for them?
- Where does the translational component for more basic research into application fit in, and should it be included?

Group 3:

- There are lessons to be learned from the US model. It is important to connect with them and apply our own context.
- A similar model was developed by another group, by getting about 20 people around the table who started by creating a charter/MOU and outlining some of the responsibilities of each player.
- One question is how to manage or balance that from a local perspective and then, based on larger organizations, how to involve all levels.
- How often would the network meet (e.g., annually?).
- A core group could be developed for decision making that could link to other groups (e.g., the Ontario Brain Institute) that are already building networks.
- A national environmental scan may be needed to see what networks are already out there, how they are working, and whether their infrastructure could be utilized or not.
- A strategy for priority setting and decision making is needed.
- Sustainability is an important consideration: what is being sustained—the network itself or the work it is recommending?
- Centres of expertise need to be identified and a decision made about whether universities would continue to be a key base for experts.
- How would local service-providers be incorporated into this? Financial or other support may be needed to involve them, as not everyone can be expected to work off the side of his/her desk.
- How would the "bubbling up" process occur, and what role would political decision-makers play (e.g., current "hot topics")?
- The peer-review process and tapping into expertise is vital.
- The process by which smaller studies would potentially move to the next scale needs to be clarified.
- Interest from other CIHR Institutes and linking to them (e.g., through populations of interest) needs to be explored.
- Knowledge translation is an integral piece of this effort and should be built into the network up front. The CCTN has some potentially useful software.

Key Discussion Points:

- The CCTN is, itself, evaluated by researchers.
- *Where* treatment takes place is important (e.g., pharmacological interventions might not be the same as secondary prevention ones). There will need to be some adaptability based on which service-providers are involved.
- Protocols must be developed for research studies by researchers and service-providers together.
- In terms of bringing ideas forward, NIDA has a Community Epidemiology Work Group composed of local intelligence agents that don't use the classic survey method but meet once or twice a year and produce an annual report.
- The new network could also serve as a data collection system.
- Trials have to follow certain protocol; they have to be designed, described, and steering and trial-management committees have to be struck. Anything that moves too quickly won't reach the necessary level of evidence, and we will wind up answering questions quickly but with sub-optimal data.
- The network is aimed at building capacity around trials research in addiction and using the community to engage real questions and real people.
- It takes 16 years to put knowledge into practice. If the focus is only on relevant, pragmatic clinical trials, the network will always be out of date.
- It is important that this initiative delivers on its promises. If local authorities think they can come to the network for a quick answer, our reputation will suffer when they don't get one. This can't serve all purposes to all people; initially we need to show the validity of the network at producing impactful results.
- Alcohol and gambling are also addictions, so we should keep the focus broad and not solely on drugs.
- It is important to be pragmatic and focus on priorities, but the reality is that some trials may benefit from industrial partners (e.g., pharmaceuticals).
- A lot of research has been done at the top of the pyramid, using the traditional RCT approach, but it is at the middle level that innovation and rigorous, multi-site evidence is most needed. This shouldn't be limited to clinical interventions but could include community-based, targeted, or other types as well.
- We need to move away from the term "addiction". The network should be designed for and most receptive to interventions that have the greatest impact on reducing risk and burden of disease from substance abuse.

- We need some early successes in order to develop capacity and build the network to the point where we can ask bigger questions.
- The bubble test should be whether it is doable, feasible, and also ready to go.
- There are many models to choose from. Maybe we should issue smaller grants (e.g., $40,000) and see who comes up with the best concept.
- We need to put more thought into the nodes/teams and whether they should be based on geography, expertise, or a combination of both.
- Many networks are clustered around diseases. If synergies can be created, we might be able to save money by pooling infrastructures and energy.

Dr. Phillips noted that most provinces have already applied for funding through the Strategy for Patient-Oriented Research to establish research support units. The units will be responsible for methodologies, statistics, data management and analysis, and training. Depending on how quickly they develop, it may be possible to use them to reduce some of the network's infrastructure costs.

Closing Remarks

Dr. Phillips wrapped up by thanking the workshop organizers, participants, and speakers—in particular, Dr. Tai, for coming such a long way to share her insights with the group. He commented that, while $7 million alone would not solve the need for more research on addiction prevention and treatment, if would at least initiate the creation of an infrastructure capable of attracting the necessary resources.

Many questions around the creation of the network, he said, were a matter of semantics—in particular, the definition of a "clinical trial". While RCTs could be a component of what the network's efforts, he said, the focus would be on identifying promising interventions that had not attracted appropriate support or evidence to date but showed good potential if adopted.

In keeping with Dr. Tai's "take home" message about being modest in terms of how much infrastructure support is provided directly to the network, Dr. Phillips said that INMHA planned to spend approximately $250,000 per node. That, he said, should be sufficient to foster their creation while at the same time leaving enough money to test a

few of the most promising interventions. The resulting successes would then be used to justify larger future investments.

Dr. Phillips agreed that sustainability was important but maintained that the network should have a typical 7- to 10-year lifespan in order to give new ideas and initiatives a chance. He added that he hoped the network would be sufficiently complementary to the CCTN that, where possible, it might participate in some of its trials—as well as feed the results of some its own work into the American network.

Dr. Phillips expressed confidence that, if structured properly at the outset, the Canadian network would open doors and create opportunities for larger-scale collaborations in the future. He promised to provide participants with ongoing updates and invited their continued input on the proposal as it was drafted into more concrete form.

Appendices

Appendix 1: Agenda

Monday January 21st (Day 1) – Chateau Laurier – Canadian Room		
Time	**Activity**	**Speaker**
8:30 – 9:30	**Breakfast –Canadian room**	
9:30 – 9:45	Opening Remarks	Anthony Phillips
9:45 – 10:45	Presentations (2)	Cécile Benoit Adrienne Stevens & Matthew Young
10:45 – 11:00	**Networking Break**	
11:00 – 12:15	Presentations (2)	Bernard Le Foll Pierre-Paul Rompré
12:15 – 13:15	**Lunch – Canadian Room**	
13:15 – 15:00	Presentations (2)	Benedikt Fischer Kathryn Gill
15:00 – 15:15	**Networking Break**	
15:15 -17:00	Presentation (1)	Betty Tai

Tuesday January 22nd (Day 2) – Chateau Laurier – Canadian Room		
Time	**Activity**	**Speaker**
08:00 – 09:00	**Breakfast – Canadian Room**	
09:00 – 10:30	Presentations (3)	Richard Dubras Patricia Conrod Samir Khan
10:30 – 10:45	**Networking Break**	
10:45 – 12:00	Breakout session – What Should a Canadian Clinical Trials Network Look Like?	All
12:00 – 13:00	**Lunch – Canadian Room**	
13:00 – 14:00	Future Directions	All
14:00 – 14:15	Concluding Remarks	Anthony Phillips

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