

Centre for Addiction and Mental Health

Research Report 2001/2002

A Pan American Health Organization / World Health Organization Collaborating Centre
Affiliated with the University of Toronto



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Contents

LETTERS

- 4 From the President and CEO
- 5 From the Vice-President, Research

Extramural Funding

- 6 SOURCES OF EXTRAMURAL RESEARCH FUNDING
- 7 BREAKDOWN OF EXTRAMURAL FUNDING BY SOURCE

Departments

- 8 NEUROSCIENCE RESEARCH DEPARTMENT
- 10 Biobehavioural Pharmacology
- 13 Biopsychology
- 15 Clinical Neuroscience
 - Clinical Neuroscience I
 - Pharmacological Modulation of Addiction-Related Cognitive Networks and Related Processes
- 18 Human Neurochemical Pathology Laboratory
 - Drug Use
 - Movement Disorders
- 19 Laboratory of Cellular and Molecular Pathophysiology
- 20 Molecular Neuroscience
 - Molecular Neurobiology I
 - Molecular Neurobiology II
 - Molecular Physiology
- 24 Molecular Pharmacology
- 25 Neuroimaging
- 26 Pharmacogenetics
- 27 Psychiatric Neurogenetics
 - Psychiatric Epigenetics
 - Psychiatric Genetics
 - Psychiatric Pharmacogenetics
- 29 Smoking and Nicotine Dependence
- 31 Transgenic Facility
- 32 VIVIAN M. RAKOFF POSITRON EMISSION TOMOGRAPHY CENTRE

34 CLINICAL RESEARCH DEPARTMENT

- 36 Addictions
- 37 Mood and Anxiety
- 38 Personality and Psychopathology
- 40 Psychobiology of Aggression and Antisocial Behaviour across the Lifespan
- 42 Schizophrenia
- 44 SOCIAL, PREVENTION AND HEALTH POLICY RESEARCH DEPARTMENT
- 46 Culture, Community and Health Studies
- 48 Health Systems Research and Consulting
- 50 Ontario Tobacco Research Unit
- 51 Population and Life Course Studies
- 53 Regulatory Policies and Legal Controls
- 55 Social Factors and Prevention Interventions
- 57 Women's Mental Health and Addiction

Honours, Appointments and Awards

- 59 HONOURS, APPOINTMENTS AND AWARDS

Grants and Contracts

- 62 GRANTS AND CONTRACTS

Publications

- 71 Books
- 71 Book Chapters
- 72 Refereed Articles

Research Staff

- 84 Conferences and Presentations
- 85 Scientists
- 85 Trainees
- 86 Students
- 86 Support Staff
- 88 Other Staff
- 88 Volunteers

Letters

From the President and CEO

THE CENTRE FOR ADDICTION AND MENTAL HEALTH (CAMH) will soon celebrate its fifth anniversary since the successful amalgamation of its four founding organizations. Since the merger, CAMH has focused on its four pillars: its academic teaching role and creating better understanding, prevention and care in the fields of mental health and addiction.

Quality care includes not only treatment, but also education, prevention, health promotion and research. Under the leadership of Dr. Franco Vaccarino, our research at CAMH has been very successful.

Through the commitment, generosity and support of our scientists and partners, research in addiction and mental health at CAMH has thrived and continues to aspire for excellence. We collaborate successfully with local, national and internationally recognized neuroscientists, clinical and social scientists and offer first-rate facilities, a range of professional training and a province-wide network of community program staff. Partners such as Canadian Institutes of Health Research, Canadian Foundation for Innovation and Ontario Innovation Trust play a key role in facilitating and supporting innovative research at CAMH. Our researchers take great pride in developing world-class research and clinical “bed-side” care.

Over the last fiscal year, researchers and scientists of CAMH obtained hundreds of grants, produced publications and

presented at scientific conferences all over the world. In that year, our total extramural funding increased 13 per cent, to over \$27 million. This achievement, along with increases over the past few years, has generated an enormous level of energy and progress within various areas of the organization.

With ongoing support and commitment from our partners, staff, researchers and scientists, our research program will continue to grow and excel in the future — especially as we prepare to redevelop the Queen Street site. The proposed site redevelopment plans envision a facility that is a vibrant urban village, connected with various stakeholders inside and outside CAMH.

As we move forward, our foremost priorities are, as always, our commitment to excellence and client-centred care. We look forward to continued support from our generous partners and to additional opportunities for forming new relationships.



Paul E. Garfinkel, MD, FRCPC
President and Chief Executive Officer



From the Vice-President, Research

COMMITMENT TO RESEARCH EXCELLENCE HAS NEVER BEEN stronger at the Centre for Addiction and Mental Health (CAMH). The breadth and excellence of our research is reflected in the many innovative new projects and partnerships, increased funding, and a variety of other opportunities that have been realized by our researchers and scientists over the past year.

Our work with various funding agencies — including Canadian Institutes of Health Research, Canadian Foundation for Innovation and Ontario Innovation Trust — is stronger than ever and will continue to grow in the future. Our scientists and researchers have been very active in communicating and sharing their new findings, at over 640 conferences in 146 cities in 28 different countries, in the past year. This dedication and renewed commitment to collaborating on and promoting research allows CAMH to play a leadership role locally, nationally and internationally.

This last year also marked the beginning of the planning process for our new site redevelopment. Through this process, our research staff were involved in planning the expansion of the research program and relocation to a new state-of-the-art research facility. This exciting new proposed facility would house CAMH researchers and create an environment aimed at fostering research collaboration and integration between our various departments and programs.

Through various extramural funding successes we have been able to continue to develop the our research infrastructure. Examples of this success include the establishment of a new confocal microscopy facility that will enable researchers to view intracellular structures and processes with extremely high resolution. Another example is the new state-of-the-art three-dimensional positron emission tomography (PET) camera. This new PET camera will allow researchers to examine neurochemical activity of the living human brain, with unprecedented precision and specificity. These tools will be key to the future as we continue to uncover the neurobiological underpinnings of mental illness and addiction, while also strengthening our understanding of the full human, social and community dimensions of these health problems.

The following pages provide an overview of CAMH research, as well as highlights of key research activities over the past year.



Franco J. Vaccarino, PhD
Vice-President, Research
Centre for Addiction and Mental Health
Professor, Departments of Psychiatry and Psychology
University of Toronto



Sources of Extramural Research Funding

These organizations have generously supported the Centre's Research Initiative. Without their valuable funding, our advances in research would not have been possible. The Research Office gratefully acknowledges additional support from the Associates in Psychiatry.

Addiction Therapies Inc.

Alberta Heritage Foundation for Medical Research

Alzheimer's Association

AstraZeneca

Aventis Pharmaceuticals Inc.

Bill Jefferies Schizophrenia Endowment Fund

Canada Foundation for Innovation

Canada Mortgage and Housing Corporation

Canadian Diabetes Association

Canadian Music Therapy Fund

Canadian Psychiatric Research Foundation

Canadian Tobacco Control Research Initiative (National Cancer Institute of Canada)

Central East Mental Health Implementation Task Force

Central South Mental Health Implementation Task Force

Centre for Social Research on Alcohol and Drugs

Change Foundation

Connaught Foundation

Crohn's and Colitis Foundation of Canada

Cyberonics Inc.

Delex Therapeutics

Distress Centres of Ontario

EJLB Foundation

Eli Lilly Canada Inc.

Government of Canada

Canadian Institutes of Health Research

Canadian Institutes of Health Research, Institute of Neuroscience, Mental Health and Addiction

Canadian Population Health Initiative

Citizenship and Immigration Canada

Health Canada

National Health Research and Development Fund Program

Natural Sciences and Engineering Research Council

Social Science and Humanities Research Council

Government of Ontario

Ministry of Community and Social Services

Ministry of Education and Training

Ministry of Health and Long-Term Care

Ontario Administration of Settlement and Integration Services

Ontario Substance Abuse Bureau

Hospital for Sick Children

Huntington Study Group

Ian Douglas Bebensee Foundation

Innovus Research Inc.

Janssen Pharmaceutical Inc.

Juvenile Diabetes Foundation (International)

London Mental Health Crisis Service

Lundbeck Canada Inc.

The Maytree Foundation

Merck Frosst Canada Inc.

Muskoka-Parry Sound Community Mental Health Services

National Alliance for Research on Schizophrenia and Depression

National Cancer Institute of Canada

National Centre for Responsible Gaming

National Crime Prevention Centre

National Institutes of Health

National Institute on Alcohol Abuse and Alcoholism

National Institute on Drug Abuse

National Institute of Mental Health

National Parkinson Foundation

Network of Centre of Excellence

Neuromolecular Inc.

New Brunswick Ministry of Health

Niagara Health System

Niagara Partners in Service

North Atlantic Treaty Organization

Northeastern, Grand River District Health Council

NV Organon

Ontario Fire Marshals and Public Safety

Ontario HIV Treatment Network

Ontario Hospital Association

Ontario Innovation Trust

Ontario Mental Health Foundation

Ontario Neurotrauma Foundation

Ontario Problem Gambling Research Council

Ontario Round Table on Appropriate Prescribing

Open Society Institute

Pakistan Institute of Learning and Living

Parkinson Foundation of Canada

Pfizer Canada Inc.

Robert Wood Johnson Foundation

Schizophrenia Society of Canada

Scottish Rite Schizophrenia Research Program

SmithKline Beecham Pharma Ltd.

Smokeless Tobacco Research Council

The Society for Progressive Supranuclear Palsy

Stanley Research Foundation

Status of Women Canada

University of Rochester

University of Toronto

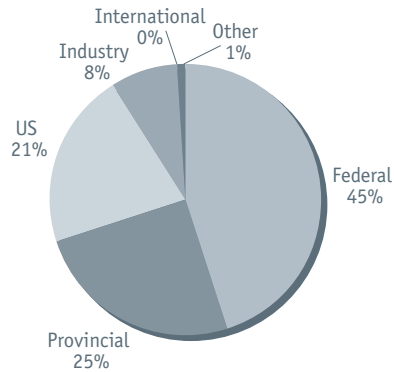
York University

Younger Foundation

Breakdown of Extramural Funding by Source

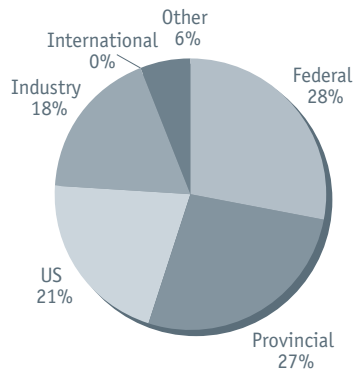
2001–2002

Federal	\$ 12,288,174
Provincial	\$ 6,995,445
US	\$ 5,775,143
Industry	\$ 2,262,987
International	\$ 20,080
Other*	\$ 362,283
Total	\$ 27,704,112



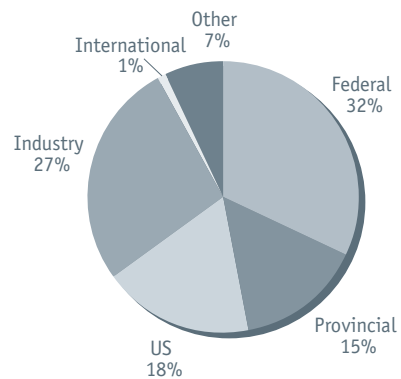
2000–2001

Federal	\$ 7,024,820
Provincial	\$ 6,522,371
US	\$ 5,056,829
Industry	\$ 4,333,412
International	\$ 72,643
Other	\$ 1,454,755
Total	\$ 24,464,830



1999–2000

Federal	\$ 7,082,642
Provincial	\$ 3,227,968
US	\$ 3,917,452
Industry	\$ 5,753,959
International	\$ 138,193
Other	\$ 1,480,251
Total	\$ 21,600,465





Neuroscience

RESEARCH DEPARTMENT

DR. JAMES KENNEDY, DIRECTOR

MENTAL ILLNESS AND ADDICTION WILL continue to affect people's lives the same way until research reveals the mechanisms involved in these disorders. Understanding how alcohol, other drugs and psychiatric problems affect the human body and brain is crucial to the development of more effective approaches to treatment and prevention.

The Neuroscience Research Department focuses on neurobiological mechanisms underlying mental illnesses, addiction and their respective treatments. The Neuroscience Research Department benefits from state-of-the-art, in-house research facilities. These facilities include the Positron Emission Tomography (PET) Centre, which allows researchers to scan the brains of live human subjects, and the Transgenic Research Centre, which can alter the genetic makeup of laboratory mice to mimic human diseases such as schizophrenia, bipolar disorder or addiction.

Each neuroscience research section has its own health theme and neurobiological emphasis. We are investigating how variations in the action of dopamine — a “neuro-transmitter,” or chemical that allows signals to pass

- 10 Biobehavioural Pharmacology
- 13 Biopsychology
- 15 Clinical Neuroscience
 - Clinical Neuroscience I
 - Pharmacological Modulation of Addiction-Related Cognitive Networks and Related Processes
- 18 Human Neurochemical Pathology Laboratory
 - Drug Use
 - Movement Disorders
- 19 Laboratory of Cellular and Molecular Pathophysiology
- 20 Molecular Neuroscience
 - Molecular Neurobiology I
 - Molecular Neurobiology II
 - Molecular Physiology
- 24 Molecular Pharmacology
- 25 Neuroimaging
- 26 Pharmacogenetics
- 27 Psychiatric Neurogenetics
 - Psychiatric Epigenetics
 - Psychiatric Genetics
 - Psychiatric Pharmacogenetics
- 29 Smoking and Nicotine Dependence
- 31 Transgenic Facility

between cells in the brain — have been linked to a range of problems, from schizophrenia, bipolar disorder and Parkinson’s disease to dependence on alcohol, cocaine, nicotine, and amphetamines. Disturbances in signal transduction and molecular and genetic mechanisms within cells are also of great interest, and are now believed to be critical determinants of mental illness and addiction. Examining the genes for neurotransmitters, and other systems known to be involved in drug response, may lead us to predict the type and amount of medication best for each individual patient. Pharmacogenetics, the study of how genes relate to drug response, may also help to predict those people who are at higher risk for addictions.

By exploring these research strategies, researchers within the Neuroscience Research Department broaden our understanding of mental illness and addiction and lay the basis for potential new treatments of the future.

The following pages show how the work of our neuroscientists is recognized throughout the world, and how we are making enormous strides toward unravelling the complexities of mind and brain. Our diverse research is well integrated, and a rich cross-fostering of ideas is evident in innovative combinations of methods across the department. One example of this integration is our recent initiative that combined molecular genetics, epigenetics, and PET scans to simultaneously assess the human brain’s blueprint and biologic activity in depression and in Parkinson’s disease. Following forward from our initial pilot studies linking PET images to genetic variants, we now have the world’s largest collection (more than 250) of DNA samples from patients who have undergone PET scans.



In the past few years, we have focused on consolidating and building on the strengths of our neuroscience research group, and establishing future priorities. In the months and years to come, neuroscience will gain increasing importance in the education, clinical and research activities of the Centre. The growth and activities of our department have been incorporated into the Functional Plan for the new Queen Street site development, which promises more space and resources to further enhance our world-class efforts in neuroscience research and training.





Biobehavioural Pharmacology
NEUROSCIENCE RESEARCH DEPARTMENT

DRS. A.D. LE & DENISE TOMKINS, HEADS

The research goals of the Biobehavioural Pharmacology Section are: to understand the underlying behavioural and neurobiological mechanisms that initiate and maintain alcohol dependence; and to use this understanding to explore therapeutic agents for treating alcohol dependence. The majority of our research focuses on issues related to alcohol's reinforcing ability and relapse to alcohol drinking behaviour with an emphasis on the role of stress in relapse. We continue to explore the role of specific central neurochemical systems in regulating these behavioural processes, in addition to examining the possible role of genetic factors involved in problem drinking and concurrent problems with other substances, such as nicotine.

During the past year, we have increased our knowledge of the role of specific neurochemical systems within the brain that regulate alcohol consumption in general, as well as identified potential systems that may predispose an individual to problem drinking. We have begun to explore sex differences in susceptibility to alcohol's effects, with a particular emphasis on cognitive function, which is an increasing public health issue. We hope our research will, in time, help develop therapeutic agents, identify potential risk factors, and provide research-based information on alcohol's effects on the brain and its ability to function.

Stress and Relapse to Alcohol

Relapse is a major challenge in treating alcohol dependence. Exposure to stressful situations has been identified as a key factor in relapse to alcohol use. A major research effort in the section attempts to elucidate neurochemical mechanisms underlying stress-induced relapse to alcohol.

Over the past year, we have advanced our understanding of the mechanisms of stress-induced relapse. Using our animal model, we found that the brain neuropeptide involved in the co-ordination of stress responses, corticotrophin releasing factor (CRF), plays a critical role in stress-induced relapse to alcohol. Administration of a CRF receptor antagonist can block stress-induced relapse to alcohol; these CRF receptor antagonists may potentially be used to treat alcohol dependence.

CRF might control relapse to alcohol by interacting with a specific serotonergic pathway in the brain. Such a serotonergic pathway has been shown to play a significant role in inhibitory control of behaviour. A number of CRF receptor antagonists are currently being developed for treating anxiety and depression.

Co-Abuse of Alcohol and Nicotine

Another finding is the mechanism underlying the co-abuse of alcohol and tobacco. We have shown previously that nicotine can enhance alcohol self-administration in experimental animals, and treatment with a nicotinic receptor antagonist can reduce alcohol consumption. Genetics have been shown to play a critical role in problem alcohol use in humans. We have found that there might be a common genetic determination for alcohol and nicotine abuse. Animals selectively bred for high alcohol consumption also self-administer more nicotine than those bred for low alcohol consumption.

Of most interest to our researchers is our finding on the effect of exposure to nicotine on alcohol consumption. Animals exposed to nicotine for a short period during their adolescence have a much higher preference for alcohol when tested during adulthood. This effect of nicotine is age-dependent, as similar treatment with nicotine in adult animals did not affect alcohol consumption when tested three months later.

This finding is consistent with the notion that nicotine might act as a "gateway" drug.

5-HT Receptor Subtypes and Alcohol Reinforcement Processes

Multiple neurotransmitter systems help to modulate the impact that alcohol has on the behaviours linked to problem alcohol use and alcohol's dependence liability. We have been selectively manipulating central neurotransmitter function in animal models of alcohol drinking behaviour. We hope to further our understanding of the neurobiological mechanisms underlying excessive alcohol consumption.

Studies in humans and animals suggest an association between the central neurotransmitter, 5-HT, and problem alcohol use and dependence. We continue our work to assess how modulating activity at various 5-HT receptor subtypes affects alcohol self-administration behaviour.

One receptor of particular interest is the 5-HT_{1B} receptor. Human studies have suggested that a locus that predisposes people to antisocial alcoholism is linked to the 5-HT_{1B} receptor gene. Over the past year, we have clearly demonstrated that 5-HT_{1B} receptors play an important role in regulating alcohol intake in our animal models. So far, this effect of the 5-HT_{1B} receptors appears limited to substances with pharmacological activity, such as alcohol and cocaine, because consumption of other fluids and other general behaviours are less sensitive to effects of 5-HT_{1B} receptor manipulations.

We continue to study two brain areas, the amygdala and the ventral tegmental area, that may be important in mediating 5-HT_{1B} receptor effects on alcohol intake. Results to date suggest that activation of 5-HT_{1B} receptors within the ventral tegmental area lead to a decrease in alcohol intake, while in the amygdala, the same manipulation leads to an enhancement of alcohol intake.

These differential findings in discrete brain regions demonstrate that the regulatory effect of 5-HT_{1B} receptors within the brain is site-specific. Furthermore, the data on the amygdala is particularly intriguing, as very few reported pharmacological manipulations have increased alcohol intake in animal models. Our findings may suggest that the amygdala exerts an important modifying influence on alcohol consumption, under normal circumstances, that can be reversed by activation of 5-HT_{1B} receptors within this area.

We are continuing this line of research in the hopes of better understanding the neural circuitry important in regulating drinking behaviour.

GABA_a Receptor Subunits, Drinking Behaviour and Voluntary Intake

Compelling evidence suggests that central GABAergic systems play an important role in regulating alcohol's effects, particularly those effects mediated via the GABA_a receptor.

We continue to investigate regional differences in the expression of the GABA_a receptor subunits. These differences have been demonstrated in the brains of high-alcohol preferring rats, and humans with drinking problems. These differences might represent one of the neurobiological factors underlying problem alcohol use.



Previously, we found significant differences in the GABA_a receptor between animals with a propensity to self-administer alcohol and those without. We found support in reports of altered brain, cerebral spinal fluid and plasma GABA levels associated with alcohol dependence and withdrawal and in reports of altered GABA_a receptor binding, and region- and subunit-specific changes in GABA_a receptors, in the brains of people who are alcohol-dependent. A tentative link between various GABA_a receptor subunit genes and a risk for alcoholism may be related to differences in the expression of alcohol's behavioural effects.

This ongoing project combines behavioural and biological approaches to investigate if higher levels of GABA_a receptor subunits within discrete brain loci are a predictor and/or a consequence of high-alcohol drinking behaviour. Much of the research on neurochemical effects of alcohol has used force administration. We consider potentially crucial differences between "self-administered" versus "experimenter-administered" alcohol, as different neurochemical systems may be involved in voluntary drug-seeking behaviour and in forced intake, the former being more analogous to drug-taking by humans.

The data generated thus far demonstrate that regional differences in GABA_a receptor expression and subunit conformation also affect the binding profile of some pharmacological agents that interact with this receptor complex, including muscimol, flunitrazepam and diazepam, but not others, such as zolpidem. There appears to be a complex interaction between inherent alcohol preference, alcohol drinking history and the binding ligand employed. Currently, we are analysing and interpreting the extensive database generated over the last year. These data will provide important insights not only into the genetic and non-genetic GABA_a receptor influences on alcohol preference and consumption, but also on potential interactions with and/or influences over other clinically used pharmacological agents that interact with this receptor complex, such as the benzodiazepines.

Sex Differences in Susceptibility to Alcohol-Induced Cognitive Deficits

We are studying the differences in alcohol's effects on brain function in men and women. In our work, we hope to unravel some of the gender differences in susceptibility to alcohol-induced cognitive impairments and provide new knowledge about the role of GABA_a receptors in these impairments. Ultimately, this research could help identify risk and/or protective factors for alcoholism specific to women and help develop effective treatment and prevention strategies. Over the past year, we began to explore the long-term effects of alcohol exposure on cognitive function and behaviour, with specific emphasis on examining potential differences in susceptibility between males and females.

Clinical evidence suggests that women are more vulnerable to the negative effects of alcohol than men are, even when doses are adjusted for body composition. In addition to being more susceptible to alcohol-related diseases (e.g., liver damage), women appear to be more sensitive to the cognitive deficits induced by long-term alcohol exposure. For example, women are more impaired during tasks demanding divided attention or delayed recall, even when blood alcohol levels are comparable to those of men. Interestingly, in tests of psychomotor performance, males and females have been consistently reported to be equally impaired following alcohol ingestion.

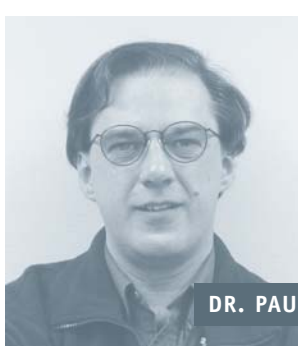
Despite the urgency of attending to such critical sex differences, alcohol research has customarily employed males (humans and animals) to avoid the hormonal confounds introduced by the female estrous cycle. However, research to date has found no consistent evidence that alcohol-induced impairments differ over the female menstrual cycle.

Furthermore, in animal studies where sex differences have been studied, investigators have not considered sex differences in the pharmacokinetic profile of alcohol. Females have generally been exposed to equivalent, or even higher, doses compared to their male counterparts during these studies. Functionally equivalent doses of alcohol were not administered in these studies, as females (both animal and human) generally achieve higher blood alcohol levels due to sex differences in body composition. This limits the interpretability of these data.

Our recent studies were designed to examine sex differences in susceptibility to ethanol-induced impairments of cognition. In these studies, the doses are titrated to ensure that equivalent blood ethanol levels are achieved in both sexes over an extended period of time. We are currently testing the following hypotheses:

1. Female rats will require lower doses of ethanol to be administered to achieve similar blood ethanol levels to that observed in their male counterparts.
2. On measures of psychomotor performance, female and male rats will be equally impaired following acute and chronic exposure to equivalent functional levels of ethanol.
3. Females will show greater impairments on measures of spatial learning and delayed recall compared to their male counterparts when exposed to equivalent levels of ethanol over an extended period of time. These sex differences will not necessarily be observable during acute ethanol exposure, but will be observable both in the ethanol-free state following chronic ethanol exposure, and following a subsequent ethanol challenge test.
4. Females and males will not show impairments under experimental conditions that assess sensorimotor ability and motivation during the spatial learning and delayed recall tasks, demonstrating that differences in performances between the sexes are due to cognitive deficits, and not other factors such as their inability to complete the task due to motor deficits, visual deficits and overall motivation to perform the task.
5. Chronic exposure to functionally equivalent levels of ethanol in male and female rats will result in differential alterations in GABA_A receptor subunit expression in a sex-, brain region- and subunit-specific manner. Furthermore, these differences in brain regions implicated in cognition are correlated with the deficits observed on measures of spatial learning and delayed recall.

Our data thus far support our hypothesis that sex differences in some, but not all, behaviours occur when equivalent blood alcohol levels are maintained over an extended period of time. This first step in the project confirms the validity of our test regimen. Over the coming year, we will expand on this pilot data and specifically explore sex-related differences in alcohol's long-term effects on cognitive function.



Biopsychology

NEUROSCIENCE RESEARCH DEPARTMENT

DR. PAUL J. FLETCHER, HEAD

The Biopsychology Section focuses on the role that brain neurotransmitter systems play in controlling behaviour. We are particularly interested in the serotonin and dopamine systems, and the interactions between these systems. Our general strategy is to use pharmacological and/or lesioning procedures to manipulate specific aspects of neurotransmitter function, and to observe the resulting changes in behaviour. Our current studies explore neurochemical mechanisms involved in addictive behaviours, cognitive behaviours relevant to schizophrenia and the mode of action of antipsychotic drugs.

Serotonin and Drug Use

A long-standing project in the Biopsychology Section explores the consequences of altered serotonin function on reward-related behaviour, with special emphasis on drug-seeking behaviour. Over the past two years we have been especially interested in the role of a specific serotonin receptor subtype, the 5-HT_{2C} receptor, in modulating the behavioural effects of drugs of abuse.

5-HT_{2C} Receptors and Cocaine

We previously found that stimulation of 5-HT_{2C} receptors, with the 5-HT_{2C} receptor agonist Ro60-0175, attenuated a variety of behavioural effects elicited by cocaine, including cocaine self-administration.

We have now determined that blocking the activity of 5-HT_{2C} receptors enhances the effects of cocaine. Specifically, the 5-HT_{2C} receptor antagonist SB242,084 increases the locomotor stimulant effect of cocaine, increases intravenous self-administration of cocaine and potentiates cocaine's ability to induce relapse to cocaine-seeking in subjects whose self-administration behaviour has been extinguished. Our complementary findings with 5-HT_{2C} agonists and antagonists demonstrate that 5-HT_{2C} receptors exert a bi-directional influence over the expression of the effects of cocaine.

The 5-HT_{2C} receptor is expressed in a part of the brain, the ventral tegmental area (VTA), that gives rise to the mesolimbic dopamine pathway, which is critically involved in mediating the effects of many drugs of abuse. Our most recent findings indicate that injecting the 5-HT_{2C} receptor agonist Ro60-0175 into the VTA reduces cocaine-induced locomotor activity, and cocaine self-administration. Serotonin, acting via 5-HT_{2C} receptors, modulates the effects of cocaine specifically in the VTA, perhaps by indirectly altering the function of the mesolimbic dopamine pathway.

5-HT_{2C} Receptors and Other Drugs

A parallel series of studies examined the effects of 5-HT_{2C} receptor blockade on the locomotor stimulant effect of several other drugs of abuse, including amphetamine, phencyclidine, morphine, nicotine, and methylenedioxymethamphetamine (MDMA). The receptor blockade SB242,084 significantly increased the activation induced by all of these drugs. The effect was most pronounced in the case of MDMA. MDMA releases both serotonin and dopamine. The fact that 5-HT_{2C} receptor blockade greatly enhances the stimulant effect of MDMA could indicate that, under normal circumstances, serotonin acting via the 5-HT_{2C} receptor subtype might inhibit the activating effects of MDMA. Removal of this inhibition then leads to greater activation.

5-HT_{2C} Receptors and Addiction

The 5-HT_{2C} receptor has several different polymorphisms and isoforms. We have observed that 5-HT_{2C} receptor blockade leads to exaggerated responses to drugs of abuse. This indicates that individual differences in 5-HT_{2C} receptor function could be one neurobiological mechanism underlying vulnerability to addiction. We recently found, in collaboration with Dr. Peter Clifton (University of Sussex, England), that mice lacking 5-HT_{2C} receptors show an increased behavioural response to MDMA. Thus, we have evidence that a genetic alteration in 5-HT_{2C} receptor function has an identical effect to pharmacological blockade of 5-HT_{2C} receptors.

Models of Schizophrenia: Amphetamine Sensitization

In a different line of research, we have been collaborating with Dr. Shitij Kapur and Dr. Catherine Tenn (Schizophrenia Research Division, CAMH) to explore the usefulness of amphetamine sensitization as a model for schizophrenia. Repeated amphetamine use can induce psychosis in humans, while in animals the behavioural responses to amphetamine are augmented, or sensitized, with repeated use. Some people with schizophrenia show augmented DA release, as inferred by a greater shift in the binding of [³H]raclopride following a challenge with amphetamine. As well, some people with schizophrenia exhibit a disrupted prepulse inhibition of the acoustic startle response, which is thought to reflect altered information processing.

We have shown that these behavioural and neurochemical abnormalities are also present in rats exposed to a sensitizing regimen of amphetamine. Thus, amphetamine sensitization could be a useful model for understanding pathophysiological mechanisms in schizophrenia, as well as mechanisms of action of antipsychotic drugs.



Models of Schizophrenia: Damage in the Prefrontal Cortex

Dysfunctional dopamine activity is linked to schizophrenia, and schizophrenia is a neurodevelopmental illness. We know that the mesolimbic dopamine system is modulated by the prefrontal cortex, including dopamine elements within the prefrontal cortex. We have begun to explore the effects of early damage to dopamine in the prefrontal cortex on adult behaviour. To date, we have found that even modest damage to dopamine projections to the prefrontal cortex has repercussions for the expression of adult behaviours. In particular, early-life damage to prefrontal cortex dopamine appears to greatly facilitate the development and expression of amphetamine sensitization.



Clinical Neuroscience

NEUROSCIENCE RESEARCH DEPARTMENT

DR. USOA BUSTO, HEAD

Many factors influence compulsive drug-taking behaviours. These factors vary according to the drug, the host and the environment. The Clinical Neuroscience Section studies the behavioural and pharmacological effects of drugs in humans and the different factors that may contribute to drug-taking behaviour.

CLINICAL NEUROSCIENCE I

DR. USOA BUSTO

Host Factors Contributing to Substance Use Disorders

A major line of our research explores host factors contributing to substance use disorders, including multiple drug use, psychiatric comorbidity and genetics.

We continue to examine the role of the brain reward system in major depressive disorder (with Drs. Claudio Naranjo, Helen Mayberg and Simon Graham). Our findings suggest that dopamine and the brain reward system are dysfunctional in severely depressed patients and that specific areas of the brain are involved in the response to a dopaminergic probe. In a neuro-imaging study, which is the logical continuation of the brain reward system clinical study, we are currently looking at the specific areas of the brain where changes in the response to amphetamine actually occur.

Another area of our research explores the role of nicotine in modulating symptoms of depression in depressed smokers and non-smokers (with Drs. Laura Cardenas, Martin Zack, Sylvain Houle, Shitij Kapur and Helen Mayberg). Preliminary data from positron emission tomography (PET) studies suggest that dopamine release in depressed smokers was significantly lower in comparison to depressed non-smokers. This suggests a hypo-functional brain reward system in people with depression. Age is another host factor contributing to substance use disorders. We are studying the effects of hypnotic medications in older adults (with Drs. Beth Sproule and Nathan Herrmann). We hope to document the advantages and disadvantages of prescription versus non-prescription sleeping medications in an older adult population.

Prescription Drug Dependence

Pain and depression may influence dependence on opioid medications, particularly prescription opioids. This year, we started a collaborative study with the Clinical Research Department, examining the characteristics of, and comorbid disorders in, patients dependent on prescription opioids. Our findings, which have been recently presented, show that there are four patterns of opioid abuse: Heroin only, prescription drugs only, prescription drugs and heroin (current) and prescription drugs with a past history of heroin abuse/use. The prescription-only patients are older and have more substantial pain and psychiatric comorbidity than all the other groups. This study will lay the foundation for future research in people who are dependent on prescription

drugs and who have comorbid problems, such as chronic pain and depression (with Drs. Beth Sproule and Bruna Brands).

Abuse Liability of Drugs

The intrinsic pharmacological characteristics of drugs of abuse (such as potency, the ability to produce reinforcing effects and drug kinetics) are essential to drug-taking behaviour. We continue to research the comparative abuse liability of currently available drugs as well as new compounds. Our ongoing work looks into the comparative pharmacology, behavioural effects and abuse potential of heroin and hydromorphone in human subjects (with Drs. Bruna Brands and David Marsh).

PHARMACOLOGICAL MODULATION OF ADDICTION-RELATED COGNITIVE NETWORKS AND RELATED PROCESSES

DRS. MARTIN ZACK AND CONSTANTINE X. POULOS

Our research explores cognitive processes that mediate self-regulation of addictive behaviour. Using a cognitive neuroscience approach, we study ways that alcohol and other drugs affect the way people — with and without addictive disorders — process information.

Psychoactive drugs can activate or inhibit the cognitive processes that regulate behaviour under normal circumstances. Our methodology consists of cognitive science tasks (e.g., reaction time, vigilance, attention, psychomotor inhibition), often administered by computers, and pharmacological probes (e.g., drugs of abuse, drugs that tap specific neurotransmitter systems).

To further our understanding of the neurochemistry underlying addiction, our general strategy is to assess how drugs modulate addiction-related cognitive networks in memory. Cognitive networks are sets of concepts linked in memory around a common theme (e.g., alcohol, smoking, gambling, panic, phobic concerns). Such networks distinguish clinical populations, including addicted people, from healthy controls. Pharmacological or environmental cues can activate these networks. Cognitive activation can then bias decisions or overt behaviour toward substance use or gambling, either directly or by engendering subjective states (e.g., negative affect, anxiety, craving) that motivate these behaviours. Because the biasing effects of cognitive activation can occur automatically and involuntarily, they may contribute to the compulsive aspects of addictive behaviour.

This is particularly important in people who have concurrent disorders, such as people who are anxious and have drinking problems, because their addiction networks may be intertwined with networks related to their anxiety disorder. It also permits us to use drug probes to evaluate gambling-related cognitions in people who have gambling problems. This approach is especially important because there are no animal models to provide information about the neurochemical basis of gambling.

Priming of Gambling-Related Cognitions by Amphetamine

In this project, funded by a grant from the National Center on Responsible Gaming, we examined how amphetamine, a psychostimulant, activates motivation to gamble and automatic gambling-related cognitions in people who have gambling problems, people who have drinking problems, and controls.

The results indicate that, in people who have gambling problems, amphetamine primes gambling cognitions; inhibits neutral cognitions; increases urge to gamble; and decreases confidence to avoid gambling. Amphetamine had no such effects in controls. Although amphetamine increased desire for alcohol in people who have drinking problems, it did not reliably alter confidence to avoid drinking, nor did it affect alcohol-related cognitions.

These findings support the possibility that gambling addiction is mediated by the same neurochemical circuits activated by psychostimulant drugs.

Priming of Alcohol-Related Cognitions by Benzodiazepines

In this project, we examine the effects of two benzodiazepines on motivation to drink and automatic alcohol-related cognitions in people who have drinking problems. We are comparing the effects of diazepam, a drug with high abuse liability, with those of clonazepam, a drug with low abuse liability. The project also examines the moderating effects of drug dose, severity of alcohol problems, and degree of co-existing anxiety on cognitive and behavioural responses to these drugs. Our findings will lay the foundation for future research, using other pharmacological probes, to better characterize the specific neurochemical substrates of motivation to drink in people who have drinking problems and varying degrees of anxiety.

Effects of Alcohol on Stress-Induced Cognitive Activation in Young Drinkers with High- and Low-Anxiety Sensitivity

This project, funded by a grant from the Alcoholic Beverage Medical Research Foundation, evaluates the effects of a moderate dose of alcohol on automatic anxiety-related cognitions induced by a stressor in university students with a high or low sensitivity to anxiety-provoking stimuli.

Anxiety sensitivity is a trait variable that also predicts the subsequent development of anxiety disorders. People with a high sensitivity to anxiety use alcohol to cope with negative mood states more often, and display higher rates of alcohol use problems, than do people with a low sensitivity to anxiety. We hope to determine a possible mediating role of cognitive activation in the negative reinforcing effects of alcohol in young people with a high sensitivity to anxiety. This may help us develop strategies to prevent or reduce the transition to full-blown comorbid anxiety and alcohol use disorders later in life.



Effects of Chlorpromazine on Smoking-Related Cognitions

In this study (a collaboration with Dr. Bill Corrigall, CAMH), we gave a low dose of chlorpromazine, a typical antipsychotic, to male smokers with no psychiatric disorder. Our intent was to evaluate the effects of chlorpromazine on the subjects' automatic smoking-related cognitions and motivation to smoke.

Our results indicate that chlorpromazine augments activation of smoking cognitions induced by overnight abstinence. This effect correlates with self-reported craving for cigarettes. Smoking a single cigarette also had a greater dampening effect on activation in subjects who received chlorpromazine than in subjects who received a placebo.

We observed a parallel pattern on a cognitive task that involved no specific smoking-related stimuli. These results indicate that information processing may contribute to extremely high smoking rates in people receiving typical antipsychotic medications.

Deficient Inhibitory Control and MDMA (Ecstasy)

In this study, funded by the Grants in Psychiatry program, CAMH, we identified a consistent linear increase in impairment of inhibition with chronic use of MDMA in people who used no other drugs. Using controls of healthy non-MDMA users, we identified empirical cut-offs for the levels of MDMA use that coincide with a significant increase in "disinhibition." This finding may provide a rough index of the point where the neurotoxic effects of MDMA begin to translate into demonstrable impairment in self-control.

Current work extends this evidence to investigate how other potentially neurotoxic drugs and marijuana may affect the impairment of people who use MDMA and these substances. (Drs. Paul Fletcher and Stephen Kish, CAMH, are collaborators on this project)

Alcohol-Gambling Associations

This study investigated the cognitive mechanisms involved in concurrent gambling and alcohol problems. Some people who gamble report a tendency to drink more when they win. These people displayed greater activation of alcohol cognitions by win-related verbal stimuli (e.g., a jackpot) than did gamblers with no specific drinking bias, or gamblers who said they were less likely to drink when they won.

Our results support the possibility that cognitive activation contributes to the motivation to drink in certain people who have gambling problems. Involuntary-gambling/alcohol associations specify a process that may explain how gambling and alcohol become linked in comorbidity and provide a target for interventions designed to treat such individuals. (Drs. Sherry Stewart and Ray Klein of Dalhousie University are collaborators on this project.)

Project funded by a grant from the Ontario Problem Gambling Research Centre (held jointly with Dalhousie University).



DR. STEPHEN KISH, HEAD

Human Neurochemical Pathology Laboratory NEUROSCIENCE RESEARCH DEPARTMENT

The mandate of the Human Neurochemical Pathology Laboratory is to understand the causes of neuropsychiatric disorders through direct examination of the human brain by either brain scan procedures in living subjects or by neurochemical investigations in autopsied human brain. During the year 2001, we published eight articles in peer-reviewed neuroscientific journals. The laboratory continues to divide its time between studies of drug use (ecstasy) and psychiatric problems in patients with movement disorders (Parkinson's disease).

DRUG USE

Ecstasy

Ecstasy (MDMA), a derivative of amphetamine, is widely used by people of all age groups worldwide. Among known risks of the drug (e.g., death in a very small number of users), the most serious concern is that ecstasy might cause permanent damage to brain neurons that use serotonin as a neurotransmitter, as suggested by animal data.

In collaboration with the PET brain scan unit at CAMH (Drs. Sylvain Houle, Alan Wilson, Natalie Ginovart), we have begun to measure the number of serotonin neurons in brain of chronic users of ecstasy as compared with that in a control group. The results of this study will help define the risks of taking ecstasy and may also help us to understand the role of serotonin in different psychiatric conditions, such as depression and panic anxiety, sometimes observed in people who use ecstasy.

MOVEMENT DISORDERS

Depression in Parkinson's Disease

Recent data suggest that depression has a greater impact on the quality of life of the patient with Parkinson's disease than does the movement disorder (rigidity, tremor, slow movement) itself. Work of Dr. Oleh Hornykiewicz suggests that damage to the brain serotonin system might explain the depression in Parkinson's disease. In collaboration with Dr. Mark Guttman (Human Neurochemical Pathology Lab), responsible for the largest Parkinson's disease practice in Canada, Dr. Jerry Warsh, a CAMH psychiatrist specializing in mood disorders, and the PET unit, we are comparing the number of serotonin neurons in brain of depressed patients with Parkinson's disease, non-depressed patients with Parkinson's disease, and control subjects. The results of this study, supported by the Michael J. Fox Foundation, will help us understand the nature, cause, and treatment of the disabling depression in Parkinson's disease.





Laboratory of Cellular and Molecular Pathophysiology

NEUROSCIENCE RESEARCH DEPARTMENT

DR. JERRY WARSH, HEAD

Research in the Laboratory of Cellular and Molecular Pathophysiology Section investigates the cellular and molecular pathophysiology of the major psychoses, principally bipolar affective disorder, and the molecular pharmacology of antibipolar and antidepressant medications. The research team includes Dr. Jerry Warsh, clinician scientist, Dr. Peter Li, senior basic scientist, and their graduate student and postdoctoral trainees.

Our groundbreaking, innovative research has led us to discover abnormalities in signalling processes inside nerve cells. These abnormalities play a critical role in the development of bipolar I disorder.

A year ago, we identified patterns of changes, in several genes and their protein products, that affect intracellular calcium signalling in a subtype of bipolar I disorder. This year, we identified two novel target genes whose expression is regulated by lithium treatment; these genes may represent therapeutically relevant targets of this medication.

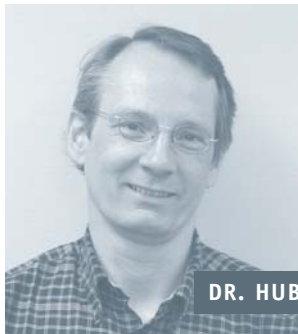
Inositol monophosphatase type 2 is an enzyme found to be altered in cells from people who have bipolar disorder. Lithium, a mainstay in the treatment of bipolar disorder, blocks the activity of this family of enzymes. Using special gene-hunting techniques, our research team continues to identify genes that may be affected by lithium and other mood stabilizers. This year, we identified a gene that encodes diphosphoinositol polyphosphate phosphohydrolase, an enzyme that helps metabolize inositol polyphosphates. We identified another gene that encodes a transmembrane-4-superfamily protein, CD151. This is a scaffolding protein that interacts with several signalling molecules in the inositol lipid signalling pathway.

These observations clearly support lithium's therapeutic potential to regulate the expression of a distinct set of genes involved in the signalling pathway(s) known to be dysregulated in bipolar disorder.

Our findings of the past year continue the current goal of our research — to translate our findings into clinical tests to more easily diagnose subtypes of bipolar disorder; and to predict which patients will respond to lithium or other mood-stabilizing medications.

Our research grants, awarded by the Canadian Institute for Health Research and the Ontario Mental Health Foundation, now total \$1,295,000. These grants allow our lab to conduct the studies necessary to produce clinical tests for use at the bedside and in the community. Our findings also set the stage to develop new drugs for treating and preventing relapses in bipolar disorder. The closer we come to understanding the specific chain of cellular disturbances that lead to this disorder, the more effectively we can work to develop new strategies to treat and prevent it.





DR. HUBERT H.M. VAN TOL , HEAD

Molecular Neuroscience

NEUROSCIENCE RESEARCH DEPARTMENT

The goal of the Molecular Neuroscience Section is to understand the mechanisms by which neural communication takes place. By taking a deterministic approach to fundamental problems in neurotransmission, we seek to understand the molecular components involved in communication between neurons and how these components may contribute to mental illness and how they serve as therapeutic target.

The section has three principal investigators directing their own research group. Their research involves molecular, biochemical and electrophysiological approaches to study the molecules involved in neuronal signalling. Our scientists principally apply *in vitro* approaches and use model systems, including transgenic mice and the nematode *C. elegans*, for their research. They often extend their findings to human disease through collaboration with other scientists, most notably with the Neurogenetics Section at CAMH. The research section is widely associated with many neuroscientists inside Toronto (<http://www.uoftphysiology.com/neurosciencenet/governance.html>), and outside Toronto, and is associated with the CNHR group *The Synapse* (<http://www.utoronto.ca/synapse/>).

MOLECULAR NEUROBIOLOGY I

DR. HUBERT H.M. VAN TOL

This group focuses on the dopamine signalling system in the central nervous system. This system is often presumed the origin, and/or one of the main targets for therapeutic intervention, for the symptoms of several psychiatric and neurological disorders, including schizophrenia, bipolar disorder, Huntington's disease, Parkinson's disease, Tourette's syndrome, addictions and attention deficit hyperactivity disorder. We hope to understand the individual components involved in the dopamine signalling system, so we can evaluate how the system contributes to development of disease, improve therapeutic interventions and minimize treatment side-effects.

In humans, the neurotransmitter dopamine is synthesized in the brain in neurons located in the midbrain area, most notably the substantia nigra and the ventral tegmental area. These neurons project to their target areas where dopamine is released in a regulated manner. The importance of proper function of these neurons is seen in examples such as the loss of dopamine neurons of the substantia nigra, which is the cause for Parkinson's disease. Evidence is emerging that excessive dopamine release plays a role in schizophrenia, and in the study of addiction, several drugs of abuse have been found to stimulate dopaminergic transmission.

Dopamine released from these neurons binds to specific targets known as dopamine receptors. Five different dopamine receptors have been identified in humans; these receptors are all members

of the G-protein-coupled receptor (GPCR) family. Besides the target (postsynaptic) neurons, dopamine receptors are also present presynaptically on the dopamine neurons themselves. Thus dopamine neurons can serve as a component of the feedback mechanism for controlling their own release.

Activation of the dopamine receptors by the neurotransmitter will activate a cascade of intracellular signalling molecules. This cascade will ultimately mediate a change in the activity of various ion channels or modulate the status or expression of the molecules involved in neurotransmission, thus modulating the excitability of the cell and the transmission of a signal. Many areas are still poorly understood, such as the factors controlling dopamine neuron development, regulation of neurotransmitter release, and mechanisms of dopamine receptor-mediated changes in intracellular signalling.

Novel Dopamine Signalling Pathways

Dopamine receptors belong to the superfamily of receptors that mediate their signal through heterotrimeric G-proteins. Evidence is emerging to show that this family of receptors may also directly interact with other cellular components that will either regulate the receptor or serve as effector. We identified that dopamine receptors can bind Src homology 3 (SH3) domains. SH3 domains can be found in a variety of proteins involved in intracellular signalling, and these domains serve a role in bringing proteins together in the cell. Using yeast two-hybrid and phage displays screening protocols, and more directed protocols, we have been identifying SH3-domain-containing proteins that can directly interact with dopamine receptors.

We and others have observed that this type of interaction may modulate receptor internalization and the activation of mitogen-activated protein kinases (MAPK). Our observation has directed our research on the functional significance of this interaction into these two areas. In past study, we found that dopamine D2 and D4 receptors activate the MAPK pathway through transactivation, a process by which platelet-derived growth factor receptors are activated. In collaboration with Dr. John F. MacDonald (Department of Physiology, University of Toronto), we found that transactivation is also critical for the mechanism by which dopamine receptors can reduce N-methyl-D-aspartate (NMDA) activation in hippocampal neurons. The mechanism of transactivation is not well understood and is the subject of our ongoing studies. The observation that dopamine receptors can transactivate growth factor receptors, and thus a large variety of intracellular signalling pathways, may give us new insight in how dopamine receptors control neuronal development and survival, differentiation, and synaptic plasticity.

GIRK Channel Complex

G-protein-activated inwardly rectifying K⁺ channels (GIRK; a.k.a. Kir3) are the effector of various GPCRs, including the dopamine D₂, D₃ and D₄ receptors. Four different Kir channel subunits, Kir3.1, 3.2, 3.3 and 3.4, form a tetrameric complex to make a functional channel. These channels regulate the excitability of the cell by maintaining the membrane potential to the resting potential. The presence of these channels in the presynaptic dopamine neurons, particularly Kir3.2, may play an important role in the feedback regulation of dopamine release through its activation via presynaptic dopamine D₂ receptors.

We know that these channels are activated in a membrane-delimited manner, arguing that the channel and receptor have to be close to each other to mediate functional activation. However, we do not know the precise nature of the channel receptor relationship. We used molecular and biochemical approaches to show that the dopamine receptor and GIRK channel form a stable complex early during their synthesis. The stability of the receptor-channel complex does not depend on receptor activation or G-proteins, but its initial formation depends on G-beta-gamma G-protein subunits.

In collaboration with Dr. Terrence Hebert (Montreal Heart Institute, University of Montreal) we used bioluminescence resonance energy transfer in live cells to extend these findings to other receptors, including the beta 2-adrenergic receptor. The observation that the receptor-channel complex is stable may help us understand how temporal control of synthesis of the individual components regulates GPCR-activation of different signalling pathways. Our ongoing work investigates the molecular determinants of this interaction.



Model Systems: *C. elegans* and Dopamine Signalling

The nematode *C. elegans* is a model system that can be analysed with powerful genetic tools. Its genetics, anatomy, development, behaviour and nervous system have been well studied. By mammalian standards, *C. elegans* has a very simple nervous system. However, it encodes most of the known molecular components of mammalian brains.

We confirmed that *C. elegans* produces dopamine and several of its metabolic products. Others identified several key components of the dopamine system, including tyrosine hydroxylase and the dopamine transporter.

The dopamine receptor of *C. elegans* remains elusive. Using bioinformatic approaches we identified up to 15 candidate dopamine receptors. One of these receptors encodes on functional and pharmacological grounds for a dopaminergic receptor. In collaboration with Dr. Joseph Culotti (Samuel Lunenfeld Research Institute, Mount Sinai Hospital, Toronto), we identified the neurons in *C. elegans* that express this receptor and mutant strains in which the receptor is disabled.

With Dr. William Schafer (University of California, San Diego), we observed that mutant strains with this receptor disabled displayed an altered habituation response to non-localized mechanical stimuli (“tap response”). This is consistent with the observation that this receptor is expressed in the mechanosensory neurons ALM, PLM and PHC. We are analysing these mutant strains, using genetic suppressor screens to identify genes linked to the dopamine receptor functioning. This way, we hope to identify new components involved in the functioning of the dopamine signalling system. Based on the observed genetic similarities between humans and *C. elegans*, these genes may fulfill a similar role in the functioning of the mammalian dopamine system.

Model Systems: Candidate Genes for Schizophrenia Using a Rodent Model System

Schizophrenia is a complex genetic disorder best reflected by a multiplicative multilocus model. Its complexity is a huge challenge for genetic studies, a challenge best met by using candidate gene analysis in family-based association studies. Candidate genes for these studies are mainly selected on the basis of their role in development or the functioning of the dopamine system or on the basis of being a target for drugs inducing psychosis. Current molecular technologies, particularly micro-array technologies, allow for the rapid screen of the expression of many genes. Genes with an altered expression in schizophrenia may be labelled as candidate disease genes.

We collaborated with Dr. Barbara Lipska et al. (Clinical Brain Disorders Branch, NIMH) to pursue a non-human model system for schizophrenia (Lipska et al., 1993) to screen for candidate genes. This model contains not only the appropriate behavioural abnormalities, but also the delayed development component and differences in genetic susceptibility for the disorder. We screened up to 30,000 genes for six different parameters of the model. This allowed us to identify several genes that may be involved in schizophrenia. Several of the identified genes are being analysed in ongoing genetic family-based association studies in collaboration with Drs. James L. Kennedy and Fabio Macciardi (Neurogenetics Section, CAMH).

To date, we have found that one of the 14-3-3 genes, a multi-functional protein involved in intracellular signal transduction in neurons, shows an association with schizophrenia.

MOLECULAR NEUROBIOLOGY II

DR. FANG LIU

This year, our lab focused on characterizing the molecular mechanisms by which G-protein-coupled dopamine D₁ receptors exert functional cross-talk with ligand-gated ion channel NMDA receptors. Previously, we found that dopamine D₁ receptors modulate NMDA glutamate receptor-mediated functions through direct protein-protein interactions. Two regions in the D₁ receptor carboxyl tail can directly and selectively couple to NMDA glutamate receptor subunits NR1-1a and NR2A. More significantly, we found that one interaction is involved in the inhibition of NMDA receptor-gated currents, and the other is implicated in the attenuation of NMDA receptor-mediated excitotoxicity.

D₁ Receptors Modulate Excitotoxicity

We have found a constitutive coupling between the dopamine D₁ receptor carboxyl tail and the NMDA receptor NR1-1a subunit. Interestingly, the D₁: NR1-1a binding competes with the physical coupling of the calcium binding protein CaM to the NR1-1aCT in a concentrated and Ca²⁺-dependent manner. Agonist stimulation of D₁ receptors, which protect cells from NMDA-mediated excitotoxicity, leads to the uncoupling of the D₁: NR1-1a complex, thereby leaving NR1-1a subunits more accessible to promote the formation of the NR1-1a: CaM: PI-3 kinase complex. The NR1-1a: CaM: PI-3 kinase complex can promote PI-3 kinase activity and attenuate NMDA receptor-mediated excitotoxicity.

Our study appears to be the first to define and demonstrate the possible functional implications of the interactions between the NMDA receptor and PI-3 kinase. This finding provides complementary evidence that our previous observation — that the dopamine D₁ receptor attenuates NMDA receptor-induced toxicity — does not depend on the reduction of Ca²⁺ influx but depends upon the PI-3 kinase and the subsequent activation of downstream anti-apoptotic signalling pathways, such as Akt.



D₁ Receptors Modulate NMDA Receptor Currents

Agonist-induced sequestration of plasma membrane G-linked receptors is the primary mechanism by which these receptors are desensitized. Research shows that agonist stimulation leads to D₁ receptor internalization. Collaborating with Dr. Yu-Tian Wang (professor and HHMI International Scholar, University of British Columbia), we found that the direct protein-protein coupling between dopamine D₁ and NMDA receptors enables activation of D₁ receptors to induce a rapid internalization of NMDA receptors from the plasma membrane surface, thereby reducing NMDA receptor-mediated currents. Moreover, D₁-stimulated NMDA receptor translocation can be antagonized by co-expressing the mini-gene that is able to interrupt the D₁: NR2A interaction.

These data suggest that NMDA receptor activity may be modulated via rapid trafficking away from the cell surface plasma membrane. This is consistent with the notion that NMDA receptor-mediated responses may be a product of the number of synaptic receptors.

MOLECULAR PHYSIOLOGY

DR. XIAN-MIN YU

The pathophysiological process underlying the development of schizophrenia remains a mystery for modern medicine. Data obtained from clinical and basic research studies have convincingly indicated that abnormal NMDA receptor activity is an important factor involved in the development of this disorder.

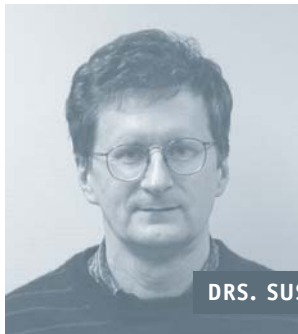
Through our research, we hope to be able to characterize mechanisms underlying the activity-dependent neuroplasticity associated with physiological and pathological processes in the central nervous system (CNS). To try to discover how neuronal activity regulates synaptic responses in the CNS, we have tried to identify the novel intracellular mediator(s) that couple the neuronal activity to the modulation of neurotransmitter receptor functions.

In the CNS, Src-family protein tyrosine kinase regulation of NMDA subtype glutamate receptors has been found to play an important role in learning and memory, ethanol sensitivity, and epilepsy. However, we do not yet understand the mechanisms underlying this regulation. We found that Src protein tyrosine kinase, its activator, protein tyrosine phosphatase alpha (PTPa) and substrate, NMDA receptors, are linked by the same scaffold protein, post-synaptic density 95 (PSD95). Through the distal phosphatase domain (D2), PTPa binds to the PDZ2 domain of PSD95. Removing PTPa does not affect the association of Src with NMDA receptors, but it may knock out the constitutive regulation of NMDA receptors by Src-family protein tyrosine kinases. Furthermore, our work demonstrates that application of PTPa functional domains (D1+D2) into neurons enhances NMDA receptor-mediated synaptic responses. Conversely, blocking endogenous PTPa inhibits NMDA receptor activity and the induction of long-term potentiation (LTP) in hippocampal neurons.

The regulation of ligand-gated ion channels, such as NMDA receptors, by protein kinases and phosphatases has been extensively studied. According to previous studies, protein kinases and phosphatases appear to act in opposition when regulating ligand-gated ion channels (i.e., kinases up-regulate, while phosphatases down-regulate, the channel activity). However, our present study gives the first direct evidence indicating that a phosphatase may also up-regulate ligand-gated ion channel functions and excitatory synaptic transmission in the CNS. PTPa is the first phosphatase found to be actively involved in LTP induction. To understand activity-dependent neuroplasticity in the CNS, it is essential to further characterize mechanisms underlying the function of PTPa in LTP induction (*The EMBO Journal*, 2002).

Another ongoing project in the Molecular Physiology group is the collaborative research with Dr. Fang Liu's Molecular Neurobiology II group. We are investigating the regulation of NMDA channels by a novel protein-protein binding interaction between dopamine D1 receptors and ligand-gated ion channels, exploring the theory that different types of neurotransmitter receptors modulate each other via their direct binding interaction (see page 22).

Our findings have created new avenues to advance our understanding of the regulation of NMDA receptor functions in the CNS. We believe that further studies will help us understand mechanisms underlying normal in vivo NMDA receptor activity in the CNS. Such understanding is essential for developing novel therapeutic approaches to treat a wide range of clinical problems such as mental illness.



Molecular Pharmacology NEUROSCIENCE RESEARCH DEPARTMENT

DRS. SUSAN R. GEORGE AND BRIAN F. O'DOWD, HEADS

During the past year, the Molecular Pharmacology Section continued work on the biology of neurotransmitter receptors for dopamine, opioid peptides, apelin and others that we identified, including the ability of the receptors to interact directly with other receptors to alter signal transduction. We have continued investigating receptor-gene-deleted mice models and models over-expressing neurotransmitter/neuropeptide to study the role of the individual receptors in brain function. Our search for novel human genes resulted in the identification of several novel receptors. Many of these are highly expressed in brain. They are potential targets as candidate genes in neuropsychiatric disease and may lead to the development of novel drugs. During the past year, we have published 13 peer-reviewed papers on our research in this section.



Receptor Biology

Almost 10 years ago, our laboratory discovered that receptors for neurotransmitters, such as dopamine, function not as individual molecules, but as highly ordered complexes on the cell surface. This discovery has been substantiated and shown to be true for all members of the family of G-protein-coupled receptors.

We also discovered that individual receptors can form complicated higher-order structures with other receptors, greatly enlarging the complexity of novel functional therapeutic targets in the brain.

We are now investigating receptor-receptor interactions, using functional assays we developed, to establish the physiological roles of this process in receptor and cell function.

We have determined the sites of interaction between two interacting receptors, and have narrowed this to a particular region of the receptor. We are intensively studying the dopamine (5 distinct receptors, D1 to D5) and opioid (3 distinct receptors) receptors and a novel receptor that we cloned, the apelin receptor. The

dopamine receptors form homomeric and heteromeric (i.e., mixtures of receptors) complexes. The apelin receptors have a highly novel expression in the cell — we are further investigating this. After activation by the specific neurotransmitter, the receptors on a cell or neuron undergo a process by which they become insensitive to further activation, termed desensitization. We have recently identified the specific amino acids within the D1 receptor responsible for this effect, in distinction from other amino acids that mediate the internalization of the receptor from the cell surface into the interior.

Novel Receptor Genes

Our successful work on the discovery of novel receptor genes has resulted in the identification of ~50 additional ones to date, many of which are expressed highly in human and rat brain and will form novel drug targets. Our laboratory and many others worldwide are conducting the physiological characterization of these receptors. We are searching through genomic databases and DNA of people with neuropsychiatric diseases for mutations and polymorphisms in the receptor genes that may predispose humans to disease.

Role of Receptors in Behaviour

Our development of several mouse models lacking individual or multiple receptor genes has proven to be an extremely valuable strategy to determine the complete repertoire of functions mediated in the brain.

Mice lacking the D1 dopamine receptor lose their preference for alcohol drinking and for sugar pellets. They appear unable to perceive rewarding stimuli and will not press a lever to obtain these substances. They also have a spatial learning deficit and an inability to forget fearful events.

We have developed a colony of D3 dopamine-receptor-lacking mice. These mice show less anxiety on some behavioural tests.

The loss of both D1 and D3 receptors prevents the manifestation of reduced anxiety, implicating an interaction between these two receptor systems in mediating the level of anxiety. We have engineered a mouse model overexpressing apelin. At present, we are characterizing the regions of brain where this is occurring and will investigate the behavioural consequences.



Neuroimaging

NEUROSCIENCE RESEARCH DEPARTMENT

DR. JOSÉ N. NOBREGA, HEAD

In the Neuroimaging Section, we aim to identify specific brain areas, neuroanatomical pathways and chemical mechanisms involved in neuropsychiatric disorders. This is done through detailed post-mortem analyses of anatomically preserved brains from animal models or human subjects. Research continues in three major areas.

Models of Depression

We are analysing brain alterations in four different models of depression, in particular the role of thyroid hormones and their receptors in brain. We continue to study models involving reactivity to stress as well as genetic models provided by collaborators from McMaster University, the University of Maryland and the Federal University of São Paulo. These analyses are complemented by similar investigations of the effects of various types of antidepressant interventions, including sleep deprivation, on the same brain systems and pathways.

In the chronic mild stress anhedonia model, we have found significant and widespread decreases in the expression of alpha thyroid hormone receptors in brain. When animals were treated with the antidepressant imipramine, both the behavioural deficits and brain receptor changes reverted to normal levels. These brain changes were not seen in the helplessness model of depression, suggesting that they may be associated with specific types of depressive symptoms.

Brain analyses in these models were expanded with the introduction of cDNA microarray techniques for large-scale gene screening.

We have reported upregulation and downregulation in a number of genes in the frontal cortex of animals showing vulnerability to depressive symptoms after stress. Unexpectedly, we found that a different set of genes was affected in animals showing resistance to depressive symptoms following stress.

In the sleep deprivation model, we reported the negative results of a fairly comprehensive assessment of neuropathology, using gene markers of apoptosis and autoradiographic indices of necrosis in brain. This agrees with other evidence that sleep deprivation does not induce neuronal loss.

The neuropeptide orexin has been identified as a key element in human narcolepsy. We have started to examine orexin, and have reported increases in the expression of the precursor prepro-orexin after sleep deprivation and after sleep rebound. We are currently completing *in situ* hybridization analyses of expression of orexin1 and orexin2 receptors after sleep deprivation.

Brain Dopamine and Movement Disorders

In collaboration with investigators from Hanover, Germany, a long-term project continues to build a comprehensive map of brain alterations in a genetic model of paroxysmal dystonia. This year we reported significant changes in glutamatergic AMPA



receptors in basal ganglia as well as changes in NK-3, but not NK-1, Substance P receptors in dystonic hamster brains.

We have made significant progress in our ongoing work with a model of tardive dyskinesic syndromes induced by long-term antipsychotic treatment. In collaboration with clinical researchers from the Centre's Schizophrenia Division, we have identified and reported important differences related to role of antipsychotic dose and route of administration (continuous vs. intermittent availability) in defining the risk of late-onset dyskinesic symptoms. We have also reported early gene activation data on a modified clozapine molecule. This finding is in line with the hypothesis that dopamine D2 receptor occupancy is a key factor in defining atypicality for antipsychotic drugs. However, our current work with mice lacking dopamine D1 or D2 receptors suggests that long-term dyskinesic effects must involve other factors in addition to D2 receptor occupation.

Brain Mechanisms of Compulsive Drug-Taking

For the last few years, in collaboration with a group from São Paulo, Brazil, we have been systematically investigating brain mechanisms underlying differential susceptibility to alcohol sensitization.

We have reported that animals showing differential propensity to alcohol sensitization have increased levels of D2 binding in specific areas of the limbic forebrain. We reported separately that similar changes were not seen in D1 receptors or in the dopamine transporter. We have also found and reported increased levels of NMDA binding in mice showing resistance to ethanol sensitization.

In collaboration with investigators from the Biobehavioural Pharmacology and the Pharmacogenetics laboratories at CAMH, we reported localized brain changes in 3H-flunitrazepam, and 3H-muscimol binding in animals showing a differential propensity to consume alcohol. We have not observed changes in other components of the GABA_A receptor system, including 3H-zolpidem and 3H-RO-154523 binding sites, and alpha1 or alpha6 receptor subunits examined by *in situ* hybridization.



DR. RACHEL F. TYNDALE, HEAD

Pharmacogenetics NEUROSCIENCE RESEARCH DEPARTMENT

Genetic variations in people's ability to metabolize drugs can result in therapeutic failure and unanticipated toxicity due to too much or too little metabolism of a drug. In addition to clinically used drugs, researchers of the Pharmacogenetics Section, led by Drs. Rachel F. Tyndale and Edward M. Sellers, explore the role that genetic variation in drug-metabolizing enzymes can have on metabolism of drugs of abuse. The section investigates how such genetic variation can alter the risk for specific drug dependencies and alter the amount of a drug used by dependent individuals, and focuses on identifying high-risk individuals and developing novel treatment approaches. A second line of research investigates the expression and regulation of drug-metabolizing enzymes in the brain. These enzymes can alter drug levels in the immediate vicinity of drug targets such as receptors and transporters. They are also responsible for creating toxic byproducts that may lead to neurotoxicity. CYP enzymes in the brain are both genetically variable (they exist in some people and not in others) and environmentally regulated (the levels and distributions in the brain can be altered by drugs of abuse).

Research from the section has demonstrated a number of actions that metabolic variations can have on pharmacology and dependence risk profile of specific drugs. For example, genetic variation in an enzyme could alter activation of a drug to a more potent drug metabolite of similar pharmacology (e.g., codeine activation to morphine by CYP2D6). It can also create differences in metabolic patterns via variant alleles (e.g., methamphetamine is metabolized to different toxic metabolites by some people). Genetic variations can alter metabolism of drugs in which the parent drug and metabolite have similar effects but different durations of action (e.g., flunitrazepam and CYP2C19) and it can alter the activation of a drug to a metabolite that has different pharmacology (e.g., dextromethorphan to dextrorphan via CYP2D6). Variable drug metabolism can also convert an active parent drug to an inactive metabolite (e.g., nicotine to cotinine by CYP2A6).

The Pharmacogenetics Section investigates these variations using abuse liability, epidemiological, genetic, biochemical and therapeutic intervention studies. The Pharmacogenetics Section accomplished the following research goals during 2001.

New Publication in Pharmacogenomics

Dr. Tyndale, with Werner Kalow and Urs A. Meyer, co-edited the book, *Pharmacogenomics* (Drugs and the Pharmaceutical Sciences series, Marcel Dekker Inc., New York, 2001), outlining current pharmacogenomic techniques and applications. This book includes techniques used by both academic and industrial laboratories, for both small-scale and high-throughput requirements.

Enzyme Variations, Medications and Drug Metabolism

In collaboration with Dr. Deborah Mash of Miami (Professor, University of Miami School of Medicine), we showed that ibogaine,

a drug being tested for addiction treatment, is metabolized by the genetically polymorphic enzyme CYP2D6. Treatment dose and outcomes are altered by this genetic variation — rapid metabolizers need larger doses and get better therapeutic outcomes.

The section has also collaborated with Dr. Allan Okey (Professor, Department of Pharmacology, University of Toronto) to investigate genetic variation in the aryl hydrocarbon receptor. This receptor, which is altered by smoking, regulates an enzyme involved in metabolizing antipsychotic drugs. In collaboration with researchers in Seattle, we determined the contribution of two genetically variable enzymes (CYP2C19 and CYP3A4) to the metabolism of flunitrazepam (Rohypnol®), a drug of abuse.

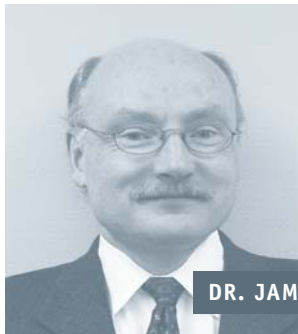
We also characterized other genetic variants of hepatic enzymes, including differences in drug metabolism for two genetic variants of CYP2D6. CYP2D6 is responsible for the metabolism of codeine and amphetamine as well as a number of clinically used drugs. We have also worked collaboratively to establish the frequencies of these genetic variants among different ethnic populations (e.g., CYP2C9).

Smoking Research

In the area of smoking research, we identified and characterized inhibitors of CYP2A6, the genetically variable enzyme that inactivates nicotine and alters smoking behaviour. These inhibitors can be used to decrease nicotine metabolism *in vivo* and to decrease smoking. We also identified the genetic variant CYP2A6*2 as being fully deficient for nicotine metabolism.

In addition, we used animal models to show that ethanol can increase the enzyme that metabolizes nicotine (CYP2B1) in the liver, and that nicotine can increase one of the enzymes that metabolizes ethanol (CYP2E1) in the liver. This work merges well with the group's ongoing investigations of the effects of ethanol on one of ethanol's target receptors, the GABA_A receptor. Using a number of paradigms, we showed that ethanol can alter ethanol metabolism and GABA_A receptor regulation (in collaboration with Richard W. Olsen, UCLA, and Jose Nobrega and Denise Tomkins, CAMH).





Psychiatric Neurogenetics

NEUROSCIENCE RESEARCH DEPARTMENT

DR. JAMES L. KENNEDY, HEAD

Genetic factors play a role in causing schizophrenia, bipolar affective disorder, anxiety disorders, alcoholism, eating disorders, autism, impulse control disorders, and some dementias. Researchers in the Psychiatric Neurogenetics Section, headed by Dr. James Kennedy, actively search for the abnormal genes involved in the cause, expression, treatment, and possible cure of these disorders. The section houses one of the world's most comprehensive collections of interview data and DNA samples from patients with psychiatric disorders, and from their families, allowing researchers to pursue diverse lines of inquiry and make extensive comparisons among mental illnesses. Aided by technology in molecular genetics, Psychiatric Neurogenetics researchers work to further our understanding of psychiatric disorders.

PSYCHIATRIC EPIGENETICS

Epigenetics deals with regulation of gene activity. It postulates that dysregulation of normal sequence genes may be as detrimental to a cell as the DNA mutations that have been the primary target of traditional genetic linkage and association studies.

Epigenetic theory unifies a wide variety of biological and psychological theories, as well as empirical findings, that pertain to major psychosis. Over the past few years, we have been intensively investigating the role of epigenetic factors in major psychiatric illness. We performed an in-depth theoretical analysis of the epigenetic mechanisms that were assumed be operating in major psychosis (Petronis, 2001).

The epigenetic principles suggested for schizophrenia and bipolar disorder can be extrapolated and applied to a wide variety of other complex non-Mendelian disorders, such as diabetes, multiple sclerosis, rheumatoid arthritis and psoriasis, among others (Petronis, 2001).

In the laboratory, we have demonstrated that even genetically identical organisms such as monozygotic twins exhibit numerous epigenetic differences (Petronis et al. in press; submitted). This finding provides the basis for a series of new explorations in phenotypic discordance (non-identity for a disease) in identical twins, an unexplained phenomenon in human biology for more than 80 years.

Psychiatric epigenetics is an innovative development in psychiatric research, and to date, we represent the only group in the world fully dedicated to this development. With the support of the CAMH Foundation we are continuing to build a comprehensive CAMH Epigenetics Research Program in psychiatric and other human complex diseases.

PSYCHIATRIC GENETICS

Three general strategies are used in the lab. In one strategy, investigators scan all the human chromosomes, using a wide array of DNA markers, in the hope of discovering a disease gene without knowing the brain processes involved. In the second, researchers test the structure of genes known or believed to be involved in the



brain function in psychiatric diseases, such as dopamine receptor or serotonin receptor genes in schizophrenia. The third strategy analyses regulation of genes; dysregulation of normal genes may increase the risk for a disease.

Candidate Genes and Attention Deficit and Hyperactivity Disorder

We have investigated numerous candidate genes for their role in neuropsychiatric disorders. In collaboration with Dr. Cathy Barr (Research Scientist, the Toronto Western Hospital), we analysed genetic variation in the genes encoding adrenergic and dopamine receptors in people who have attention deficit and hyperactivity disorder (ADHD) (Barr et al. 2001, a; b; c). Our results were consistent with those from other groups showing the dopamine transporter locus as a candidate gene for ADHD.

Phenotype for Bipolar Disorder

In bipolar disorder we examined the second messenger G-protein beta 3 subunit gene that may be involved in the action of lithium. The bipolar patients were biochemically characterized in terms of calcium homeostasis by Dr. Jerry Warsh's group. This resulted in an innovative phenotype to examine in bipolar disorder (Corson et al. 2001).

Molecular Mechanisms of Major Psychosis

With Dr. Carlos Pato (Professor of Psychiatry, State University of New York at Syracuse), we detected further evidence that the alpha 7-nicotinic receptor gene (CHRNA7) contributes to the risk of being affected with schizophrenia (Xu et al. 2001). In this study, we found that only paternal CHRNA7 is a risk factor to schizophrenia. This finding indicates the importance of epigenetic regulation in understanding the molecular mechanisms of major psychosis.



Trinucleotide Repeats in Portuguese Schizophrenia and Bipolar Patients

We continue to investigate the intriguing finding, first described by Vincent et al (2000), that unstable DNA in the form of trinucleotide repeats is increased in Portuguese schizophrenia and bipolar patients from the Azores Islands.

Serotonin System Genes and Bulimia Nervosa

In collaboration with Drs. Robert Levitan, Alan Kaplan, and Sid Kennedy, we evaluated the impact of genetic variation of the serotonin system genes (serotonin-1B receptor, *HTR1B*) on the body mass index in women affected with bulimia nervosa (Levitan et al. 2001). According to our data, we identified a possible association between *HTR1B* genetic polymorphism and body mass index. This finding may shed light on why, in response to dieting, some patients with bulimia nervosa are able to lose significant amounts of weight, whereas others have a natural limitation to their weight loss. Pending replication in a larger sample, these findings point to a possible genetic factor of fundamental importance to the bulimia nervosa population.

PSYCHIATRIC PHARMACOGENETICS

Although in its infancy, psychiatric pharmacogenetics will in the future aid clinical practice in the prediction of response and side-effects and minimize the current “trial and error” approach to prescribing medications.

Antidepressant-Induced Mania

Our group was the first to detect evidence that genetic variation in the serotonin transporter gene may account for abnormal response to medication in people with bipolar disorder (Mundo

et al., 2001). We investigated “antidepressant-induced mania,” a common side-effect in treatment of depression.

We found that carriers of a “short” version of the serotonin transporter gene exhibit a significantly higher probability of switching to a manic phase of the disease in comparison to people who carry a “long” serotonin transporter gene. A genetic test can help us identify patients at risk for the development of this potentially dangerous side-effect — a finding that will considerably improve the clinical management of bipolar disorder.

Antipsychotic Response and Side-Effects

Individual people with schizophrenia vary widely in their response and side-effects to antipsychotic medications. Using one of the best characterized samples for antipsychotic treatment response and side-effects in the world, we continued our lines of pharmacogenetic research: response to the atypical antipsychotic, clozapine; weight gain induced by clozapine; and antipsychotic-induced tardive dyskinesia, a debilitating motor system disease characterized by abnormal and involuntary movements.

We have published numerous studies examining clozapine response and DNA sequence variation across several key receptors from the serotonin and dopamine systems (Masellis et al., 2001; Ozdemir et al., 2001a, b). We evaluated the role of polymorphisms in dopamine D3 receptor (*DRD3*) and *CYP1A2* genes for propensity to develop tardive dyskinesia in patients with schizophrenia. Combining pharmacogenetic analysis of pharmacokinetic and pharmacodynamic targets for antipsychotics should improve our ability to identify subpopulations that differ in drug safety profile.

Weight gain is a serious side-effect of antipsychotic therapy. Clozapine, in particular, has the highest propensity of all antipsychotics to lead to increased weight. Because of this, we have tested if and how DNA sequence variants of the genes encoding brain receptors and the molecules involved in energy utilization are associated with susceptibility to weight gain (Basile et al., 2001).

To analyse patient susceptibility to clozapine-induced weight gain, we tested 10 genetic polymorphisms across nine candidate genes, including the serotonin 2C, 2A, and 1A receptor genes (*HTR2C/2A/1A*); the histamine H1 and H2 receptor genes (*H1R/H2R*); the cytochrome P450 1A2 gene (*CYP1A2*); the beta3- and alpha-adrenergic receptor genes (*ADRB3/ADRA1A*); and tumor necrosis factor alpha (*TNF-alpha*). We collected prospective weight gain data for 80 patients with schizophrenia who completed a structured clozapine trial. We observed promising trends for *ADRB3*, *ADRA1A*, *TNF-alpha*, and *HTR2C*.

This work is the first to provide a detailed methodological analysis of the literature on the obesity-related pathways and to develop rationale for other molecular genetic studies in this field of pharmacogenetics.



Smoking and Nicotine Dependence

NEUROSCIENCE RESEARCH DEPARTMENT

DR. WILLIAM CORRIGAN, HEAD

The long-range goal of the Smoking and Nicotine Dependence Research Section is to better understand the brain mechanisms involved in nicotine addiction and to use this knowledge to test neurochemical targets to develop medications that can help in tobacco-use cessation. The experimental design of our ongoing studies recognizes that nicotine, the primary psychoactive agent in tobacco smoke, maintains voluntary self-administration in laboratory animals. This behaviour is a core element of addiction. Using a rat model of this self-administration behaviour, we have previously shown that nicotine maintains self-administration behaviour by acting on certain brain substrates. At present, our studies have two main directions.



Neurochemistry of Nicotine Addiction

In this project, we have previously shown that voluntary self-administration of nicotine depends on the action of the drug in two areas: 1) neurons in the ventral tegmental area (VTA) of the midbrain that use the neurochemical dopamine as transmitter (these neurons have been shown to be a critical pathway in drug reinforcement processes in general) and 2) a non-dopamine system projecting to the VTA from an area in the brainstem called the pedunculopontine tegmental nucleus (PPTg). This area may be particularly involved in nicotine addiction. The action and reinforcement of nicotine in these brain regions is influenced by neurochemical systems present there. These findings have been made through micro-pharmacological manipulations of the VTA and PPTg in animals trained to self-administer nicotine.

Under the leadership of Dr. Shafiq Rahman (Research Scientist, CAMH), our research focus has moved to examine the characteristics of the neurochemical release of dopamine in laboratory animals during both voluntary self-administration and experimenter-administration of nicotine. This research relies on a technique known as *in vivo* microdialysis coupled with neurochemical detection, which allows us to sample small amounts of neurochemicals as they are released focally in the brain reward circuits. The amount of transmitter release is then quantified electrochemically. The unique strength of these studies is the combination of *in vivo* microdialysis with nicotine self-administration, a union that will allow us to make discoveries about brain mechanisms in nicotine-reinforced behaviour.

In vivo microdialysis procedures allow us to study the extracellular dopamine concentrations in the mesolimbic dopamine system during nicotine exposure in animals trained for nicotine self-administration. As control conditions, we are also measuring dopamine concentrations during nicotine self-administration and food-maintained responding. These experiments allow us to determine nicotine-specific effects on the dopamine system, apart from the response of this brain system to other drugs (e.g., heroin, cocaine) or behaviour motivated by natural reinforcers (e.g., food).

Additionally, we are characterizing the dopamine concentration during nicotine self-administration maintained on schedules of reinforcement that require animals to do different amounts of work to obtain their drug. In this way, we can elucidate the relationship between the behavioural output for a drug and changes in dopamine concentration.

Similar procedures help us monitor the changes in dopamine concentration in the mesolimbic dopamine system following systemic administration of nicotine coupled with microinfusions of cholinergic, GABA-ergic, glutamatergic, and opioid compounds into the VTA and the PPTg. These compounds have been shown to modify nicotine self-administration. Our studies in this area will explain the mode of action of these compounds on the mid-brain dopamine system.

The results of these studies will help us understand brain mechanisms involved in nicotine addiction. In particular, the research will uncover mechanisms within the mesolimbic dopamine system, possibly new mechanisms that are mesolimbic-dopamine independent. Information of this kind can support initiatives to develop medication as well as help identify risk factors for nicotine addiction.

Smoking and Nicotine Dependence

Drug Self-Administration in Animals/Pre-clinical Medication Development

We are testing particularly relevant neurochemical agents for their ability to reduce nicotine self-administration when they are administered systemically. This year, one set of experiments began examining agonists for GABA receptors. GABA is the brain's main inhibitory transmitter. We have previously found that GABA agonists delivered into the VTA or PPTg attenuated nicotine self-administration, and did so preferentially, compared to the self-administration of cocaine. In addition, anatomical data showed that nicotine may directly target GABA-containing neurons in the PPTg. For these reasons, we are exploring the efficacy of GABA agonists delivered systemically to selectively reduce nicotine self-administration. GABA agonists are also being used in human experimental studies of drug use, including tobacco smoking, as a potential target for medication development.

A similar rationale gives evidence that a particular serotonergic target may also afford a pharmacological access point to nicotine reinforcement.

In addition, we are examining whether high-dose nicotine replacement might be a useful smoking cessation approach. Our animal model is a useful means to address this issue — we can examine the effects of sustained high-dose delivery of nicotine to the experimental animals, and we can measure the effects of high-dose delivery on nicotine self-administration and relapse after removal of the drug.





Transgenic Facility NEUROSCIENCE RESEARCH DEPARTMENT

DR. HUBERT H.M. VAN TOL, HEAD

Advances in molecular and genetic research have increased our need to analyse the function of genes in physiological contexts. New technologies can easily modify genetic material in the germ line of mice or introduce new genetic material in selected tissues or organs through viral-mediated gene transfer. These technologies have given us new opportunities to study the function of genes in whole animals, extending the molecular and genetic revolution to the realm of behavioural research.

The Transgenic Facility breeds and maintains transgenic mice strains for CAMH researchers. The facility is also equipped to help scientists create their own transgenic mice strains or to employ viral-mediated gene transfer experiments. This year, the facility lent its services to researchers in the Molecular Neuroscience, Biopsychology and Neuroimaging sections.





DR. SYLVAIN HOULE, DIRECTOR

Vivian M. Rakoff Positron Emission Tomography Centre

RESearch AT THE VIVIAN M. RAKOFF POSITRON Emission Tomography (PET) Centre concentrates in the following areas: PET Methodology (Radiochemistry and PET Instrumentation); Schizophrenia; Mood and Anxiety Disorders; and Addiction. In addition to our own research, we maintain active collaboration with other scientists within CAMH and with researchers at the University of Toronto.



PET Radioligands Development

The radiochemistry group, led by Dr. Alan Wilson, continues its innovative work in radioligand development. Our new radioligand for the serotonin transporter [^{11}C]-DASB has generated worldwide interest. This serotonin transporter is the target of the selective serotonin reuptake inhibitors, medication widely used for the treatment of depression. For the first time, we can measure accurately the effects of these antidepressants on the serotonin transporters.

New projects currently under way are attempting to develop a PET radioligand for the norepinephrine transporter as well as one to image amyloid plaques in Alzheimer's disease.

PET Instrumentation

The construction of our new scanner is nearly complete. This will be the most sophisticated PET scanner in existence for brain research and will strengthen our international leadership in psychiatric PET research. Funding for the new scanner was secured by a grant from the Canada Foundation for Innovation and the Ontario Innovation Trust fund.

An internationally renowned PET physicist, Peter Bloomfield, has joined the PET Centre scientific team. His work will focus on maximizing the potential of the new scanner. He will be assisted by PET physicist Dr. Nathalie Ginovart. Dr. Ginovart has recently initiated a new series of pharmacological experiments in rodents using a stereotactic positron probe that provides temporal and spatial resolution superior to those of existing small-animal PET scans.

Investigation of the Mechanism of Action of Antipsychotics

The PET Schizophrenia research program, under the leadership of Dr. Shitij Kapur, continues to explore the role of the dopamine system in schizophrenia. This work attempts to understand antipsychotic medications' mechanism of action in the brain. We continue to link human findings obtained with PET with those obtained from animal research to give us insights in the role of the dopamine system.

We continue to find clinical benefits in the treatment of schizophrenia, such as by optimizing existing treatments and by offering new avenues for developing more effective drugs.

The Neurochemistry of Depression

Headed by Dr. Jeffrey Meyer, this program aims to investigate the neurochemical basis of symptoms for mood disorders and the neurochemical effects of antidepressant treatment.

Recent work has focused on the relationship between changes in serotonin and dopamine receptors and the specific cognitive and neuropsychological abnormalities that are observed during depressive episodes.



We are also investigating dopamine and serotonin transporter regulation. This year, we discovered that the regulation of these transporters has an important role as a vulnerability factor for low monoamines and accompanying symptoms. Treatment studies examine the mechanism of selective serotonin reuptake inhibitors (SSRIs). We are trying to establish the percentage of serotonin reuptake sites occupied during SSRI treatment and the effects of SSRIs upon post-synaptic serotonin receptors.

The Role of Serotonin in Parkinson's Disease

Dr. Stephen Kish, in collaboration with Dr. Mark Guttman, continues to apply the PET Centre's serotonin transporter radioligand to Parkinson's disease. Abnormalities of the serotonin system may explain the onset of depression often experienced by patients with this disease. This research may help elucidate the non-motor aspects of Parkinson's disease.

Investigation of the Neurochemical Sequelae of Ecstasy Use

The effects on the brain of MDMA, better known as ecstasy, remain controversial. Dr. Stephen Kish is using [^{11}C]-DASB to find definite evidence about the presence or absence of ecstasy's effects on the serotonin transporter.



Clinical RESEARCH DEPARTMENT

DR. SIDNEY KENNEDY, DIRECTOR

- 36 Addictions
- 37 Mood and Anxiety
- 38 Personality and Psychopathology
- 40 Psychobiology of Aggression and Antisocial Behaviour across the Lifespan
- 42 Schizophrenia

THE CLINICAL RESEARCH DEPARTMENT (CRD) CONTINUES to support research, treatment and education goals of CAMH through scientific publications, presentations and transfer of knowledge to evidence-based practice and to the community at large. Dr. Larry Grupp is the Clinical Research Liaison Officer, whose mandate is to identify, promote and facilitate research opportunities and collaborations between CAMH staff at all sites and between CAMH and external partners at University Hospitals and other clinical and research institutions.

During 2001/2002, the CRD has initiated and supported a variety of intra- and interdepartmental program initiatives. *Mind Mood and Mental Health*, a publication of the Mood and Anxiety program, focused on diversity and community partners in research. This publication was widely distributed in the greater Toronto area, with over 10,000 copies placed in Shoppers Drug Mart and Guardian Drugs stores, hospital waiting rooms and doctors' offices. *Clinical Guidelines for the Treatment of Depressive Disorders* were published as a collaborative CANMAT/CPA supplement on June 2001.

Through the Family Practice Mood and Anxiety Research Network, we held a conference called Psychiatric Aspects of Sexual Health in Men and Women. This led to several clinical research projects involving testosterone in depressed and non-depressed men and estrogen replacement strategies in post-menopausal depressed women.

The CRD also supported a successful conference on Psychopathy for the Psychobiology of Aggression and Antisocial Behaviour across the Lifespan Section. In addition, a joint Intrapersonal Psychotherapy Program-CRD initiative brought Dr. James McCullough for an extended visit to discuss the Cognitive Behavioral Analysis System of Psychotherapy at CAMH and Mount Sinai Hospital.

Two of the five sections (Addictions and Mood and Anxiety Disorders) underwent external reviews during the summer of 2001. A combined review of both the clinical and research aspect of the Mood and Anxiety Program was completed.

A joint effort of the Addictions and Personality sections of the CRD was successful in obtaining a grant from the Ontario Problem Gaming Foundation to study personality variables in people who gamble. The principal investigators for this grant are Drs. Peter Farvolden and Michael Bagby (Personality and Psychopathology Research Section) and Dr. Tony Toneatto (Addictions Section).

Dr. Saulo Castel obtained a CIHR Fellowship to develop measures of psychopathology in people who have concurrent substance use problems and mental illness.

Dr. Sidney Kennedy resigned from his position as Director of Clinical Research on January 31, 2002, to take up his new position as Psychiatrist in Chief at the University Health Network, University of Toronto. Dr. R. Michael Bagby, who is a Senior Psychologist and Section Head of the Personality and Psychopathology Section, assumed the role as Acting Director of the CRD.





DR. TONY TONEATTO, HEAD

Addictions CLINICAL RESEARCH DEPARTMENT

The Addictions Section conducts clinical research, both experimental and applied, in all aspects of addiction. In the past year, the section has undergone a formal internal and external review, the results of which will serve to strengthen and guide the development of our work.

Gambling Research

The Gambling Research stream, headed by Dr. Tony Toneatto, is committed to developing empirically supported psychotherapies for problem gambling, exploring the role of pharmacotherapies for problem gambling, and contributing to the knowledge of the cognitive and behavioural phenomenology of gambling. This area of research continues to attract considerable research grant funding and to establish collaborations with several scientists within CAMH and throughout Canada.

Psychopharmacology Research

The Psychopharmacology Research stream (Drs. Bruna Brands, David Marsh, Peter Selby and Beth Sproule) is committed to expanding the range of pharmacological tools to treat substance use disorders. This goal is accomplished by evaluating novel medications, integrating existing medications into treatment settings and approaches, and applying statistical methods to predict treatment outcome. Dr. Sproule is the newest scientist in our section, joining us in January, 2002. Dr. Selby was successful in obtaining funding from Health Canada for a program directed at educating pregnant woman who smoke.

Treatment Outcome Research

The Treatment Outcome Research stream consists of three clinics headed by psychologists; the goal of this group is to address comorbid addiction populations requiring specialized care.

The Anger and Addiction Clinic, headed by Dr. Lorne Korman, provides novel, empirically-supported treatments for clients with concurrent anger, aggression and substance use problems. The Dialectical Behaviour Therapy Clinic (Dr. Shelley McMain) is committed to the specialized treatment of borderline personality disorder (with or without a concurrent addiction) using the principle of dialectical behaviour therapy. The Eating Disorders and Addictions Clinic (Dr. Christine Courbasson) is developing new clinical approaches to treat concurrent eating disorders and substance use disorders. All three clinics also provide consultation and training to other mental health care professionals throughout Canada and beyond.

In addition, a new psychologist, Dr. Rebecca Dempster, has recently been recruited. Dr. McMain received a commitment of funding from the CAMH Foundation for a study treating suicidal behaviour in people who have borderline personality disorder. Recently, Drs. McMain and Korman have completed evaluating the effectiveness of dialectical behaviour therapy for people diagnosed with concurrent borderline personality and substance use disorders. This small sample pilot study has demonstrated significant benefits of DBT compared to treatment as usual for this patient sample. Drs. McMain and Korman have been presenting the results of this research at conferences and workshops throughout Canada and internationally.

Clinical Services Research

The Clinical Services Research stream (Dr. Tony Toneatto) was formed after recommendations from an external review of the existing clinical follow-up services at the Russell Street site. Clinical Services Research conducts rigorous evaluation research, both controlled and naturalistic, of individual addiction treatment programs. The goal is to improve both the content and delivery of clinical treatment and to experimentally evaluate treatment innovations. We are set to begin an evaluation of the Guided Self-Change program, one of the major clinical programs for addictions at CAMH. We hope to evaluate the treatment components to identify predictors of positive outcome and means of improving this treatment. We are collaborating with several other programs to conduct similar evaluations.





Mood and Anxiety CLINICAL RESEARCH DEPARTMENT

DR. SIDNEY KENNEDY, HEAD

Members of the Mood and Anxiety Program conduct research activities in seven areas across four Clinical Units.

Genetics

In collaboration with Dr. James Kennedy, several investigators have received funding to investigate, and have published on, genetic aspects of depression, OCD and bipolar disorder.

Epidemiology & Health Systems

In collaboration with the Health Systems Research Unit at CAMH, Dr. Sagar Parikh has focused on health care utilization across Ontario. Dr. William Gnam continues his research on the economics of mental health issues with special emphasis on the impact of psychiatric disorders on the workplace and the labour market. Dr. Robert Cooke continues to investigate “Quality of Life” issues across the bipolar and other clinical populations.

Functional Imaging

Several investigators hold CIHR funding for PET studies. Dr. Jeff Meyer has continued to use PET to study the relationship between psychiatric symptoms in depression and abnormalities in serotonin and dopamine receptors. Recently, using a novel serotonin transporter ligand developed by Dr. Alan Wilson at the PET Centre, Dr. Meyer and collaborators have completed studies involving antidepressant effects on the serotonin transporter. Drs. Helen Mayberg, Zindel Segal and Sidney Kennedy are investigating changes in brain metabolism following successful antidepressant medication and cognitive therapy. Drs. Mayberg and Michael Bagby continue to investigate the influence of personality dimensions on brain metabolism.

Psychopharmacology

During the past year a number of investigator-initiated and industry-initiated trials involving Anxiety Disorder, Bipolar Disorder and Major Depressive Disorder have been completed.

Psychological Mechanisms & Treatments

A series of CIHR-funded studies are continuing. Dr. Segal has received funding to evaluate the role of mood-linked cognitive changes in predicting prospective relapse/recurrence following either cognitive therapy or pharmacotherapy for depression. Dr. Segal is also collaborating with colleagues in the UK in an NIMH-funded randomized trial to evaluate a prophylactic intervention designed to reduce this type of mood-linked cognitive processing.

Drs. Mark Lau and Neil Rector are funded to study the roles of cognitive inhibition and rumination in mediating the patient’s ability to benefit from treatment. In addition, Drs. Rector, Peggy Richter, Michael Gemar and Eilenna Denisoff were funded to examine cognitive factors that predict successful treatment

response and relapse potential in OCD. Dr. Martin Katzman continues to draw industry support for researching novel pharmacological interventions for anxiety. Dr. Parikh continues to evaluate cognitive-behaviour therapy and psychoeducation in people with bipolar disorder.



Psychobiological Studies

Dr. Robert Levitan has received ongoing funding from a number of federal and provincial agencies to study cortisol in adult and infant populations. Dr. Roger McIntyre has received funding to study underlying mechanisms of weight gain following treatment with antipsychotic and anticonvulsant agents and is focusing his research activity on the roles of leptin and reproductive hormone changes. Dr. McIntyre is also collaborating with Dr. James Kennedy to identify candidate genes that increase the risk for weight gain.

IPT

Drs. Carolina Cristi and Bagby have received funding from OMHF to investigate patient dimensions as predictors of outcome following several antidepressant treatments. The Clinic continues to develop a database for future IPT and related research.



DR. MICHAEL BAGBY, HEAD

Personality and Psychopathology CLINICAL RESEARCH DEPARTMENT

Research in the Personality and Psychopathology Research Section examines a broad range of topical and methodological themes related to personality and psychopathology. Some of the current projects focus on: identifying alternative structures of personality psychopathology; exploring personality traits as mediating and moderating variables in treatment outcome for several disorders, including depression, anxiety and problem gambling; studying personality as a vulnerability or risk factor for mental disorders; examining the influence of acute distress on personality and its assessment; and investigating the role of neurotransmitter mechanisms in personality. The section also develops tests and instruments to assess personality and related constructs and develops strategies to assess and treat mental disorders using the Internet.

Personality and Cognitive Vulnerability and Problem Gambling

Surprisingly little is known about the personality and cognitive characteristics of people with gambling problems. In an ambitious new program of research, Drs. Michael Bagby and Peter Farvolden hope to identify personality and cognitive factors that distinguish people who remain “social gamblers” from those whose gambling activities escalate into a dysfunction or problem gambling. The long-term goal is to identify “vulnerability” factors and to develop treatments to target these vulnerabilities.

Behavioural Inhibition, Behavioural Activation, Personality and Novelty

Theorists have proposed that two, or perhaps three, basic neural circuits — behavioral activation (BAS), behavioral inhibition (BIS) and flight-fight — mediate all of our different motivations and emotions.

Our researchers are working on a project to examine the relationship between BIS and BAS sensitivity and other major empirical systems of personality and preference for novelty.

Panic Disorder, Agoraphobia, Anxiety Sensitivity and Attachment

According to current explanations of panic disorder and agoraphobia (PD/AG), panic attacks are the result of a “false alarm” combined with an over-attentiveness to internal bodily sensations and/or a tendency to catastrophize. Agoraphobia is seen as a marker for a more severe form of panic disorder.

Some evidence suggests that increased vulnerability to separation distress and/or an “insecure” attachment style may also have an important role in PD/AG. A current project examines the relative importance of individual differences in anxiety sensitivity and attachment security in panic symptoms and panic disorder.



Personality, Positive Mood and Attentional Biases in Depression

Major depressive disorder (MDD) is an extremely prevalent mental health problem with vast socio-emotional and economic costs. High rates of relapse and recurrence create a continuing challenge in the treatment of MDD. This project examines the potential role of “positive” traits, such as behavioural activation sensitivity, extraversion, ability to experience positive mood and “positive” cognitive biases, in predicting response to treatment and relapse in depression.

Childhood Adversity, Adult Attachment Style and Interpersonal Functioning in Depression

This study explores a model that relates negative childhood events and adult attachment style to interpersonal functioning in people who have depression. We hypothesize that different kinds of negative childhood events (abuse versus neglect) will be associated with different adult attachment styles (avoidant versus anxious-ambivalent). In turn, these attachment styles will be associated with different styles of interpersonal functioning in depression, with potentially important implications for treatment.

Application of the Five-Factor Model of Personality to Psychopathology

Ongoing research in this area attempts to determine whether the dimensions of personality represented by the Five-Factor Model of Personality can be applied successfully to a variety of patient samples and used to better understand the relevant neurobiology, psychopharmacology and structure of personality psychopathology.

Relationship between Stability and Change in Personality

This study attempts to find a way to reliably assess personality traits in the context of acute psychiatric illness.

We are exploring the differences between absolute and relative stability of personality traits and issues related to personality stability — ipsative and factorial stability. This project looks at such stability issues in patients with depression, before and after treatment.

Neurotransmitter Mechanisms in Modulating Dimensions of Personality

In two ongoing studies, we are working to understand the relationship between dimensions of personality and specific neurotransmitters (serotonin, dopamine and norepinephrine).

Personality as a Predictor of Recurrent Major Depressive Episodes

Many people successfully treated for depression experience a recurrent episode following several months of remission. We continue a study of the role of personality psychopathology as a contributing factor to depressive illness.

Personality, Limbic-Cortical Function and Vulnerability to Major Depression and Other Imaging Studies

We continue to explore vulnerability to depression. PET scans in patients with depression display specific patterns to induced sad mood; people who have a high score on “neuroticism” are vulnerable to develop depression. Our research examines whether never-depressed “normal” subjects with high neuroticism scores show the same response as people who are depressed or were previously depressed.

Other ongoing PET studies examine specific receptor occupancy and the relation to personality traits thought to be regulated by these specific receptors.

Personality as a Mediator of Treatment Outcome

This ongoing project examines whether different types of personality traits (dependency and self-criticism) moderate and/or mediate treatment outcome differently in three standard and empirically established effective interventions for depression (interpersonal therapy, cognitive-behavioural therapy and pharmacotherapy).





DR. LESLIE ATKINSON, HEAD

Psychobiology of Aggression and Antisocial Behaviour across the Lifespan

CLINICAL RESEARCH DEPARTMENT

Aggression and antisocial behaviour pose huge challenges and costs to perpetrator, victim, and society. To address this issue, the Psychobiology of Aggression Clinical Research Section incorporates researchers from the Child Psychiatry and Law and Mental Health Programs, permitting the conduct of this research across the lifespan. Section researchers address issues of etiology and risk (both genetic and environmental), intervention/management and knowledge transfer.

Etiology and Risk

Several investigators are attempting to unravel the etiology of aggressive and antisocial behaviour. Drs. Joe Beitchman and James Kennedy and colleagues are investigating select serotonin system genes and aggressive behaviour. They demonstrated that one form of one of the serotonin system genes was significantly more common in a group of aggressive children than in matched controls.

Approaching genetics from a different perspective, Drs. Karine Cote and Martin Lalumiere are studying the influence of birth order on paraphilias, delinquency, and aggressiveness, among other issues, and the relevance of evolutionary, social, and immunological theories to explain these influences. Their research is based on a sample of individuals adopted at birth.

Adopting an environmental perspective in a quantitative literature review, Dr. Leslie Atkinson and colleagues showed early mother-child attachment relations are consistently but moderately associated with aggression later in childhood. Research also showed that the association between parent-child relations and aggression may be strengthened by the mediating role of emotion regulation (Dr. Fiona Miller) and antisocial cognitions and attitudes (Dr. Atkinson).

Dr. Beitchman and colleagues continue to collect data in a 14-year longitudinal study of children with speech/language disorder. Investigators hope to find how speech/language disorder and other risk factors influence antisocial behaviour and substance use problems in late adolescence/early adulthood. Dr. Tracy Skilling is investigating predictors of life-long antisocial behaviour. Drs. Skilling and Christine Wekerle are studying the overlap between bullying and substance use.

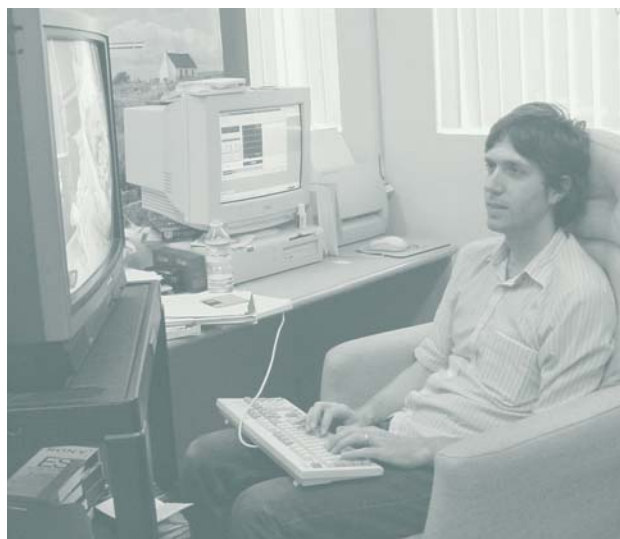
Examining more specific forms of disorder, Dr. Sherri MacKay, Joanna Henderson and colleagues are exploring mental health and specific fire-related risk factors related to juvenile firesetting. Dr. Eva Chow is investigating impulse control disorders such as kleptomania, oniomania, pathological gambling and attention deficit-hyperactivity disorder. Dr. Chow also pursues research in female sex offenders.

Dr. Howard Barbaree is examining the effects of age at release from custody on risk for sexual recidivism in sex offenders.

Intervention/Management

Dr. Miller and colleagues received funding to study the effectiveness of parent skills training and child social skills programs in moderate- and high-risk communities. Dr. Skilling is studying the design and evaluation of treatment outcomes for chronic adolescent offenders. Dr. MacKay, Ms Henderson and colleagues are preparing a randomized clinical trial to evaluate a firesetting intervention for juveniles. Dr. Wekerle is conducting a survey of child welfare adolescents along four constructs: psychiatric diagnoses, risky sexual behaviours, dating violence, alcohol and drug use. Dr. Wekerle is also evaluating a dating violence prevention program included in high school curricula in several high schools across four Canadian provinces.

Dr. David Nussbaum has standardized an instrument to assess fitness to stand trial. Drs. Cote and Barbaree are investigating the epidemiology and psychiatric, criminogenic, and social needs of individuals who are common clients of the mental health and the criminal justice systems in Ontario. Dr. Michael Seto completed a literature review on police and court diversion efforts, treatment needs, treatment, and community risk management for forensic patients. Dr. Barbaree, Dr. Seto, and colleagues are developing a model of risk management that incorporates actuarial risk, institutional treatment, dynamic risk factors, and community supervision in the prediction and prevention of sex offender recidivism.



Knowledge Transfer

Dr. Miller and colleagues received funding to study the effectiveness of evidence-based parent and child treatment programs in moderate- and high-risk communities.

Ms Henderson and colleagues conducted a province-wide study of factors affecting the acceptance and implementation of an arson prevention program for children by mental health and other community professionals. They found that implementation of “best practice” children’s mental health interventions can be enhanced by targeting professionals with particular characteristics, by designing interventions to be perceived as easy-to-use and compatible with existing practice, and by using specific dissemination strategies, including enhanced educational opportunities and ongoing “expert” support. These findings indicate that the research-practice gap can be better understood through scientific examination and that intervention developers and researchers have an important role to play in closing the gap. Dr. MacKay, Ms Henderson and colleagues are preparing a clinician’s manual for treating juvenile firesetting.

Dr. Seto chaired a committee that produced *Practice Standards and Guidelines* for members of the Association for the Treatment of Sexual Abusers.

Dr. Wekerle edited a volume integrating literatures on child maltreatment, school bullying, teen dating violence, date rape, courtship violence, domestic violence and violence among older adults with alcohol and other drug use. The book covers state-of-the-art empirical knowledge, theoretical formulations, model clinical programs, and clinical applications.

Dr. Lalumiere submitted for publication a book on juvenile delinquency.



DR. SHITIJ KAPUR, HEAD

Schizophrenia CLINICAL RESEARCH DEPARTMENT

The Schizophrenia Research Program is dedicated to a greater understanding of the “mechanisms of response” in persons with schizophrenia. We aim to determine how and why people get better and how they can best maintain their recovery. We ask this question across the spectrum of schizophrenia — from first-episode to chronic phases of the illness, across lines of gender, ethnicity and biological types. Our research effort combines contributions from all professional disciplines with the latest neuroimaging, neuropsychological and psychosocial techniques. Understanding the mechanism of schizophrenia gives us new approaches to treatment: reduced doses of antipsychotics, better algorithms for choosing antipsychotics, better augmentation therapies for patients for whom single-treatments don’t work, better group therapies and more effective educational strategies for families and patients.

Five-Year MRI Study Concludes

We recently concluded our five-year longitudinal study of comparative MRI changes in brain structure between people with schizophrenia and normal controls. The results revealed no significant brain structure changes between the groups over the study period. From this, we concluded that functional and cognitive decline in schizophrenia is not related to progressive changes in brain processes.

VCFS as a Clue to Schizophrenia

Velo-cardio-facial syndrome is a mental illness, with a known genetic defect, that presents with schizophrenia-like picture. We continue our projects examining the genetic basis of the illness and establishing how these genetic changes express themselves in psychosis. We have recently initiated a large-scale screening study to detect the incidence of this genetic defect within the Schizophrenia Program client population at CAMH.

Early Intervention in Schizophrenia

A single episode of psychosis can have a significant impact on a person’s life. We are continuing our work to prevent psychotic episodes in people showing early signs of the illness, through low dose drug treatment and supportive therapy.

Psychosocial Interventions to Enhance Outcome

Ongoing studies examine if brief, targeted education for patients and families improves quality of life and treatment adherence and, in turn, if this influences outcome. We continue to develop intervention protocols to enhance motivation. Our ongoing study, comparing psychoeducation and activity-oriented groups, continues.

Resource Use and Satisfaction among First Episode Populations

The First Episode Psychosis Program has joined with three other Ontario first episode programs to track use of available resources over a one-year period. The project will compare user rates and client satisfaction surveys between the centres. The interpretation of the data collected in this project will enable these centres to improve services and create effective new services.

How Often Do We Need to Give Antipsychotics?

Daily medication is a common part of psychiatric illness treatment. However, our brain imaging studies have shown that the effects of antipsychotics last much longer in the brain than in the blood. We have been continuing our pilot study looking into the optimal dosing frequency of antipsychotic medications. Subjects continue to receive their medications every other day for three months, then every three days for three months. At the same time, schizophrenia researchers at the PET Centre are trying to determine the best dosing interval for the new injectable “depot” atypical antipsychotics.

Augmentation Strategies to Clozapine

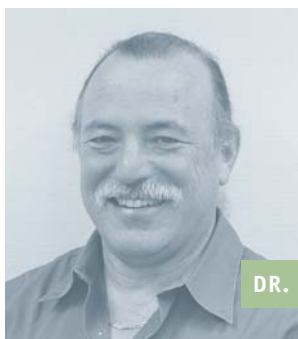
While clozapine may provide substantially improved treatment of resistant symptoms of schizophrenia, some people feel there is further room for improvement in their treatment. We have begun two new studies using medication augmentation to a clozapine treatment plan. The results of these studies may uncover more effective treatment strategies using available medications.





Magnetic Stimulation to Study Brain Defects in Schizophrenia

We have used magnetic stimulation techniques to explore how the connectivity of the different brain regions may be impaired in schizophrenia. The results show that brain regions in patients with schizophrenia show impairments in inhibiting each other, especially when patients are acutely ill. Based on our findings from these studies, we are now beginning to explore if magnetic stimulation may have a role in treating symptoms of illness.



Social, Prevention and Health Policy

RESEARCH DEPARTMENT

DR. LOUIS GLIKSMAN, DIRECTOR

- 46 Culture, Community and Health Studies
- 48 Health Systems Research and Consulting
- 50 Ontario Tobacco Research Unit
- 51 Population and Life Course Studies
- 53 Regulatory Policies and Legal Controls
- 55 Social Factors and Prevention Interventions
- 57 Women’s Mental Health and Addiction

THE SOCIAL, PREVENTION AND HEALTH POLICY Research Department conducts innovative research, using state-of-the-art methodological and statistical techniques in areas that are relevant and topical. Our research helps CAMH be among world leaders in conceptual knowledge.

CAMH has treatment, training, development, dissemination and community service functions in one organization. This allows researchers to interact directly with colleagues in other groups, providing a synergy lacking in more specialized organizations. It allows us to develop programs and services that are knowledge-based, and bring these programs and services to the community. It also allows researchers to set an agenda that responds to needs identified by the research community and by communities in Ontario.

In addition to our local research activities, many researchers in the department are engaged in international projects through the World Health Organization and other groups. The majority of our research is done with funding from external grants and contracts.

The Department contains six units: Culture, Community and Health Studies; Health Systems Research and Consulting; Population and Life Course Studies; Regulatory Policies and Legal Controls; Social Factors and Prevention Initiatives; and Women’s Mental Health and Addictions. The Department houses the Ontario Tobacco Research Unit (OTRU). In addition, we have a small core of people who conduct limited, community-based evaluations and provide evaluation consultation to community groups and agencies involved in addiction and mental health programming.





Fundamental to our mandate is that the research holds the promise of reducing the burden of harm from mental health problems and the use of alcohol, tobacco and other drugs in Ontario. Specifically, the information we produce informs the research community, the public, policy makers and program developers, through reports, conference presentations, peer-reviewed publications, position papers and media releases.

Our researchers are also often directly involved in product development, ensuring that their research is translated into effective resources. Ultimately, our work results in more effective, timely, evaluated programs and policies for mental health and addiction issues, leading to an improved health delivery system.



DR. MORTON BEISER, HEAD

Culture, Community and Health Studies

SOCIAL, PREVENTION AND HEALTH POLICY RESEARCH DEPARTMENT

Culture, Community and Health Studies (CCHS) is an integrated research, training, and consultation program. It focuses on resettlement and health of immigrants and refugees; health of First Nations peoples; cultural influences on the expression and course of illness and on the response to care; and developing models of care that are sensitive and responsive to the needs of Canada's multicultural society.

Our team includes scholars from the academic disciplines of psychiatry, sociology, clinical and developmental psychology, social epidemiology, anthropology, demography, medicine, nursing and public health. CCHS underwent its second external review in 2001. External reviewers were Dr. Lawrence Kirmayer (McGill University), Dr. William Sack (Oregon Health Sciences University), and Dr. Evelyn Bromet (State University of New York). As in our first review in 1997/1998, the reviewers in 2001 were unanimously enthusiastic about our accomplishments, and recommended the further expansion of CCHS.

Research

Over the past five years, CCHS has attracted over \$17 million in external research funding, mainly from peer-reviewed sources. Ongoing projects include studies of the health and development of immigrant and refugee children; resettlement impact and quality of life of immigrants and refugees; the role of resettlement stress in the risk of tuberculosis among immigrants and refugees; mental health in Toronto's Ethiopian and Tamil communities; the long-term effects of exposure to warfare; the mental health effects of poverty among immigrant and non-immigrant children; youth acquisition of ethnocultural identity; the mental health effects of discrimination; the role of social support in immigrant and refugee resettlement; and cultural influences on the experience and consequences of life-threatening illnesses.

Funding sources include the Canadian Institutes of Health Research, the Social Sciences and Humanities Research Council, Citizenship and Immigration Canada, Health Canada, Human Resources and Development Canada, Centre of Excellence for Research on Immigration and Settlement, and Canadian Heritage. Detailed project and staff information may be found at <http://www.utpsychiatry.com/noframes/cchs.html>.

Recent research highlights include:

- The paradoxical finding that, although immigrant families are three times more likely to be poor than non-immigrant families, immigrant children have fewer mental health and behavioural problems than their non-immigrant counterparts.
- The prevalence of depression among Ethiopians in Toronto roughly equals that found among the general population of Ontario, but is three times higher than the rates in Ethiopia.
- Social adversity and low education are strongly associated with depression among women in rural Pakistan.

- About one-quarter of visible minority immigrants experience discrimination and those experiences jeopardize mental health.
- Although female immigrants are less likely than males to receive language training in Canada, they benefit more from such training.

Education and Training

CCHS is dedicated to educating and training future generations of health researchers and health care providers who will contribute to the scholarly underpinnings for effective policy and practice. Each year, we train residents in psychiatry.

During the last academic year, Dr. Lisa Anderman was a post-doctoral fellow jointly sponsored by CCHS and the Psychological Trauma Clinic at Mt. Sinai Hospital. Under Dr. Morton Beiser's supervision, she continued her study of cross-cultural perceptions of mental health. Dr. Anderman and Dr. Tat Lo presented a well-received course in cultural competence for residents. Rani Srivastava, Director of Clinical Resources in the Faculty of Nursing at the University of Toronto, is completing a PhD at the Institute of Medical Science (IMS) under the supervision of Dr. Beiser. Dr. Kenneth Fung continued his work with Dr. Beiser on a study of alexithymia among Chinese people, in fulfilment of the requirements for a masters degree from IMS. Dr. Gerald Devins continues to supervise graduate students through IMS, including Monica Bettazonni (enhancing quality of life in schizophrenia through day-hospital programs), Sonia Sarkissian (illness intrusiveness, self-concept, and quality of life in epilepsy) and Kirsten Woodend (gender differences in illness intrusiveness and quality of life after the first myocardial infarction). Kenneth Mah continues his CIHR post-doctoral fellowship for his research on cognitive-behavioural intervention in hematologic cancer patients treated by blood and marrow transplantation.

Consultation

The CCHS unit provides community, policy and scientific consultations at national and international levels. As part of a Statistics Canada initiative, Dr. Anneke Rummens consulted on how to ask questions about ethnicity. Dr. Violet Kaspar served as a member of a National Research Council panel, Race, Ethnicity, and Health (Washington, D.C., 2001), and also served as a consultant in a Health Canada workshop for curriculum development on Health Issues, Immigration and Cultural Diversity (Ottawa, ON, 2001). Dr. Owens Wiwa participated in a speaker's platform held in Belgium (2001) to advise Greenpeace and other environmental movement and human rights organizations.



In the aftermath of the tragedy of September 11, 2001, the Canadian government distributed *Strangers Becoming Us* to the schools once again, as a tool to help children and school personnel deal with the repercussions of that singular event.

Alone in Canada, our self-help information guide developed by Dr. Laura Simich for new immigrants, is now available in English, French, Chinese, Tamil, Somali, Arabic, Spanish, Urdu, and Farsi.

Visiting Scholars

Dr. K.A.S. Wickrama, associate professor with the Department of Human Development and Family Studies and the Institute for Social and Behavioral Research at Iowa State University (Ames, IA) visited the CCHS unit for research collaboration and consultation on latent growth curve analysis for longitudinal data.

International Initiatives

The CCHS unit has been working toward developing a memo of understanding involving the University of Port Harcourt, the University of Toronto, and the Centre for Addiction and Mental Health. In the past year, this initiative, which resulted in the establishment of a Centre for Stress and Health in the Niger Delta region of Nigeria, received funding from IDRC. Another research initiative involves collaboration between the University of Toronto and the American University of Beirut for a comparative study of adolescent mental health.

CCHS as a Resource for the Wider Community

Dr. Beiser, in collaboration with the Toronto Centre of Excellence for Research on Immigration and Citizenship and Classroom Connections, developed two resource kits under the collective title *Strangers Becoming Us*. These curricula educate elementary and high-school students about the social, cultural and economic impacts of immigration on Canada, and about the mental health and other effects of resettlement on immigrants and refugees. In 2000/2001, these were distributed to all publicly funded schools across Canada.



DR. PAULA GOERING, HEAD

Health Systems Research and Consulting SOCIAL, PREVENTION AND HEALTH POLICY RESEARCH DEPARTMENT

Informing and improving systems of mental health and addiction service delivery — this is the goal of the Health System Research and Consulting Unit, the base of the University of Toronto Department of Psychiatry's Health Systems Program (formerly the Mental Health Systems Research and Development Program). An interdisciplinary team draws on the expertise of other jurisdictions, reviews current literature, interviews and consults with local stakeholders, analyses data in existing administrative databases, and gathers information through epidemiological and program evaluation studies.

To maximize the possibility of these findings being disseminated and translated into policy and practice, investigators in the unit regularly assume roles as administrators, planners, consultants and advocates to influence decision-making in the education, health care and government arenas. The unit has assumed a leadership role in this area after receiving a grant from the Ontario Ministry of Health and Long-Term Care to develop the Research Transfer Training Program. This program offered a course on knowledge transfer for the Department of Psychiatry at the University of Toronto and for CAMH researchers. The unit's consultation service is busy transferring knowledge and keeping research staff in touch with front-line service delivery issues and problems.

Members of the unit work in close collaboration with the Ontario Substance Abuse Bureau on system-related issues, such as performance measures and planning information. We have developed partnerships with provincial and federal mental health policy groups, are affiliated with the Department of Health Policy, Management and Evaluation at the University of Toronto and have developed a collaborative relationship with the Institute for Clinical Evaluative Studies. Unit staff have cross-appointments with other departments at the University of Toronto, including the Faculty of Nursing, Department of Public Health Science and the Institute for Medical Science.

Hospital Report 2001 — Mental Health Feasibility Study

As part of the Hospital Report 2001 project conducted through the University of Toronto's Department of Health Policy, Management and Evaluation, we conducted a feasibility study concerning the use of the Balanced Scorecard for hospital-based mental health care. We used literature, data and site reviews and consultation with content experts and stakeholders.

The project's final report, released this spring, evaluated the Scorecard's usefulness and feasibility for mental health care. Two modifications were recommended to improve the Scorecard's applicability. First, the indicators chosen should reflect not only the four Scorecard quadrants (system integration & change, clinical utilization & outcomes, client satisfaction and financial performance & condition) but also domains pivotal to Ontario's mental health reform: accessibility, appropriateness, outcomes,

consumer participation, and system management. Second, the scope of the Scorecard should be expanded to include provincial and regional governance levels in addition to the individual hospital or mental health/addictions unit or program.

Using these recommendations, we developed a modified framework along with example indicators, and proposed future directions for development and implementation.

Community Mental Health Evaluation Initiative

Availability of evidence on the effectiveness of different forms of community mental health support varies. A lack of common client data usually prevents researchers from comparing interventions. The Health Systems Research and Consulting Unit is the co-ordinating centre for a multi-site evaluation research project to advance understanding of the roles played by case management, assertive community treatment, crisis services and consumer and family initiatives. A cohort of over 900 individuals enrolled in 18 different programs is being assessed at three different points over an 18-month period. Most of the baseline data have now been collected and analyses are ongoing. Communications are being conducted in partnership with CMHA-Ontario. This past spring, we conducted a knowledge transfer workshop that produced "main messages" for policy-makers and the public.

Explaining Outcomes: Critical Characteristics of Community Support

Explaining Outcomes is a five-year project in the Community Mental Health Evaluation Initiative. The goal is to develop an instrument, or package of instruments, to measure the critical aspects of community support programs for people with a severe mental illness. Now in our third year of the project, the research team has developed and field tested four versions of the instrument: one for consumers, one for family members, one for service providers and one for program administrators. The next step in the project will be to pilot test the instruments, including a test-re-test of a subset of programs, to establish reliability and validity.

Comprehensive Assessment Projects

This series of needs-based planning projects originated in Ontario's psychiatric hospitals and expanded into the community system. We are using a consistent and sound methodology to assess current and recommended levels of care for people who use mental health services, and to determine how well current care matches need. Representative samples are weighted to provide data for service and system planning. To date, eight hospital and five community projects have been completed, and four are under way. We have presented our results to Mental Health Implementation Task Forces across the province.

While results vary across settings, there are some consistent findings. Most people currently using mental health services are receiving very low (about monthly) contact and a small group are receiving very high levels of support (i.e., inpatient care). Yet about half of current psychiatric hospital inpatients could be living independently in the community if intensive support were available. Additionally, about 60 to 70 per cent of people who use community-based services require more support than they are receiving. During the past few years, assertive community treatment teams have been implemented throughout Ontario, but these planning projects suggest that considerably more system capacity is needed for delivery of intensive, community-based mental health care.

Depression in the Workplace

Rising rates of disability due to depression are of concern to multiple stakeholders. In response to a request from the Ontario Roundtable on Appropriate Prescribing, we designed a study called Depression in the Workplace: Examining Antidepressant Use and Worker Characteristics and Their Associations with Disability. Three Canadian companies with national employee bases were recruited as project participants. Together, they represent over 65,000 workers.

The first findings from the Depression in the Workplace study were published in the *Journal of Occupational and Environmental Medicine*. This paper reported that as many as two per cent of the labour force will take a depression-related short-term disability leave. Depression-related leave accounts for 75 per cent of all leaves due to nervous and mental disorders. In the study sample that represented 12 per cent of the financial/insurance sector in Canada, this represented \$20.5 million in lost productivity.

A larger proportion of employees who go on short-term disability are in their mid-careers. They are people with work experience who are vital to the operation of their companies. However, the majority of people who go on depression-related short-term disability return to work rather than go on to long-term disability. People on short-term disability are not a homogenous group; for example, the severity of their symptoms varies. Effective disability management programs take these differences into account.

Best Practice for Concurrent Disorders

This project, funded by Health Canada, synthesized research literature, expert opinion and consumer focus group input to recommend improvements for community systems and services (screening, assessment and treatment/support) for people with concurrent mental health and substance use disorders.

Recommendations called for a more integrated approach at both the individual program level as well as the system level. The advice concerning specific research-based interventions differed within different clusters of concurrent disorders (e.g., mood and anxiety versus severe and persistent mental illness). The report has been completed and released by Health Canada.

Drug and Alcohol Treatment Information System

Drug and Alcohol Treatment Information System (DATIS) is a provincial information system that collects, summarizes and reports information on the volume and characteristics of people being treated for alcohol, drug and gambling problems in Ontario. Staff of the unit help select performance measures within DATIS and analyse and interpret trends that are useful for planning, accountability and research. Unit staff use the resulting databases to address research questions and report the findings in the research literature. This year, we completed the first provincial report on client characteristics and service utilization.

Systems Integration

In this project, we reviewed and synthesized findings on mental health system integration to examine strategies for creating more integrated mental health service systems, and to evaluate the effectiveness of these strategies in enhancing client accessibility, continuity and quality of care. We reviewed published and unpublished literature, looking at key studies and descriptive work. We analysed Ontario and other integration projects to identify strengths, challenges and lessons learned. We sought expert opinion by interviewing key informants and consulting with an advisory panel formed for this project.

In collaboration with the Mental Health Rehabilitation Reform Branch, the unit organized a provincial policy forum on systems integration for the Mental Health Implementation Task Forces, provincial organizations, consumers and families on October 17, 2001, in Toronto. This forum generated considerable discussion and provided advice to the Ministry on this issue.





DR. ROBERTA FERRENCE, HEAD

Ontario Tobacco Research Unit SOCIAL, PREVENTION AND HEALTH POLICY RESEARCH DEPARTMENT

Since its inception in 1993 as the research component of the Ontario Tobacco Strategy, the Ontario Tobacco Research Unit (OTRU) has been a focal point for an active tobacco control, research network in Ontario. Our principal sponsor is the Centre for Health Promotion at the University of Toronto. The Centre for Addiction and Mental Health is one of three co-sponsors of the unit, providing in-kind contributions of investigator and staff time, facilities, and administrative support. The central office of OTRU is located at the 33 Russell Street site of CAMH.

The Ontario Tobacco Research Unit is led by a multi-disciplinary team of six university-based principal investigators who spend at least 20 per cent of their time on OTRU activities. Our network also includes 35 co-investigators, 27 collaborating investigators and numerous affiliates, consultants and Ontario Tobacco Strategy partners.

Funding comes from the Ontario Ministry of Health and Long-Term Care, in-kind contributions from sponsoring institutions, and various external grants and contracts. For the purposes of this report, we have highlighted activities of the Toronto site.

OTRU's activities fall into five functional areas based on our mandates:

Program and Policy Research and Development

OTRU successfully completed its first external program review in January of 2002. According to data compiled in preparation for the review, our six principal investigators were involved in 105 unique projects under 104 research grants, 42 of which were new in 2000/2001, and produced 53 articles for peer reviewed journals. In addition to funding of \$1.4 million from the Ministry of Health and Long-Term Care, our principal investigators were awarded approximately \$1.1 million in research grants and contracts in 2000/2001.

Monitoring and Evaluation

Each year, our Monitoring and Evaluation Group produces an annual monitoring report. This report assesses areas such as smoking patterns among adults and youth, public attitudes to tobacco policies, and broad strategic issues in tobacco control. This report is central to OTRU's mandate to monitor progress of the Ontario Tobacco Strategy. Two principal sources of data for the report are the annual *CAMH Monitor* and the biennial *Ontario Student Drug Use Survey*.

Teaching and Training

We have undertaken initiatives to develop a future cadre of researchers and practitioners with particular interest in and skills relevant to tobacco control. In 2001/2002, OTRU investigators supervised individual thesis research and field practica. Drs. Roberta Ferrence and Joanna Cohen developed the

University of Toronto graduate course, Tobacco and Health: From Cells to Society. This course was also video-conferenced to the University of Waterloo via the Eli Lilly Learning Centre. This year also marked the beginning of the OTRU Studentships for Research in Tobacco Control program. We awarded 10 studentships to students across the province who committed to undertake tobacco control research projects.



Information Analysis and Dissemination

OTRU provides timely access to research materials relevant to our target audiences, principally other researchers, public health professionals and policy makers in Ontario, through the monthly mailings of our current abstracts series, literature reviews, working papers, special reports and research updates.

Networking and Communications

Since OTRU's launch in 1993, our main goal in communications and networking has been to provide a provincial focus for tobacco-related research and community health system networking. This year, we collaborated with our Ontario Tobacco Strategy partners to organize a provincial tobacco control conference for researchers, practitioners and policy makers held in Toronto in March 2002. Our website and listserv continue to provide key information on funding and research events, as well as discussion on research issues for 130 investigators and practitioners, across the province and beyond.



DR. EDWARD ADLAF, HEAD

Population and Life Course Studies
SOCIAL, PREVENTION AND HEALTH POLICY RESEARCH DEPARTMENT

The overall goal of the Population and Life Course Studies Unit is to describe the extent of addiction and mental health indicators in the population and to monitor trends. This includes: providing and disseminating accurate and timely data regarding alcohol use, other drug use and mental health indicators among general and special populations; and monitoring and identifying risk and protective factors for alcohol, other drug use and mental health indicators.

By measuring addiction and mental health indicators, we provide the knowledge base for health professionals, program planners and municipal, provincial and national government bodies. This information can also help us target prevention and other programs and evaluate existing programs, policies and health objectives. The result is an information base that helps ensure needed programs are established in a timely and cost-effective manner.

Our investigators are a multidisciplinary group comprising epidemiologists, sociologists, psychologists, criminologists and historians. Investigators also serve as experts for international agencies such as the World Health Organization and the United Nations Drug Control Programme. Unit staff hold appointments with University of Toronto departments, including Public Health Sciences, Psychology, Psychiatry, Sociology and History.

Our accomplishments during the 2001/2002 period include the following.

Student Surveys

The 13th cycle of the *Ontario Student Drug Use Survey (OSDUS)*, the longest ongoing school survey in Canada, was completed and released to the public. The *Ontario Student Drug Use Survey Drug Report* was released in November 2001, and the first *Ontario Student Drug Use Survey Mental Health Report* was released in spring 2001.

The 2001 *OSDUS Drug Report* found that, over the past decade, the smoking rate among youth has decreased. Increases in drug use stalled toward the end of this period, with the exception of ecstasy use. Still, a significant percentage of young Ontarians are engaging in risky behaviours such as binge drinking, driving after using cannabis, and being a passenger in a vehicle driven by someone who had been drinking.

The 2001 *OSDUS Mental Health Report* found that the majority of young Ontarians do not report an emotional problem, nor do they report delinquent activity. In fact, violence has decreased over the past decade.

However, the survey revealed that a significant number of youth do experience problems. For instance, just under one-third report psychological distress, one-quarter are bullied at school, and one in ten report serious thoughts about suicide and seeing a mental health professional in the past year.

Internet Resources

We completed and released our first electronic monitoring report: *CAMH Monitor eReport: Addiction and Mental Health Indicators among Ontario Adults, 1977-2000*.

The report, based on telephone surveys of adults aged 18 and older throughout the province of Ontario, describes the extent of alcohol use, drug use, mental health indicators and gambling problems, and provides a knowledge base for health professionals. The report is available at <http://www.camh.net/research/pdfs/cm2000-epirpt.pdf>.

We expanded our unit Web page, http://www.camh.net/research/population_life_course.html, to more efficiently disseminate epidemiological and other research findings. Visitors to the Web page will find our ongoing bimonthly *eBulletin*, which provides highlights of our survey research.

Self-Help Treatment of Alcohol Problems

We successfully completed an innovative NIAAA-funded study (Cunningham), which investigated the treatment of alcohol problems with self-help materials among a non-clinical sample.

The study found that those who received both self-help material and personalized feedback regarding their drinking reported significantly improved drinking outcomes after six months as compared to those who received the self-help book only, the personalized feedback only or received no intervention.



Youth, Drugs and Violence

A NIDA-funded cross national study of Youth, Drugs and Violence (Erickson), which partners with a research team at the University of Delaware, was further expanded by adding two collaborating teams from the University of Amsterdam and the University of Montreal.

This study will compare the association between violence and drug use across the four sites and among three samples of youth: students, non-students and those in detention.

Gin Use in 18th Century London

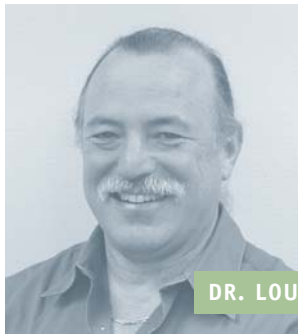
Jessica Warner completed a major scholarly publication, *Craze: Gin and Debauchery in an Age of Reason* (2002, New York: Four Walls Eight Windows).

Based on archival research funded by the American National Institute on Alcohol Abuse and Alcoholism, this book looks at gin use in 18th Century London. The ensuing “gin craze,” Warner argues, was the first modern drug scare, with parallels to more recent drug scares, including, most notably, the so-called “crack cocaine epidemic” of the late 1980s.

Gender, Alcohol and Aggression

We are collaborating with the Department of Sociology, the Centre of Criminology (University of Toronto), Department of Anthropology and Sociology (Concordia University), the Swiss Institute for the Prevention of Alcohol and Drug Problems (Lausanne) and the Addiction Research Institute (Zurich), to investigate the links between gender, alcohol and aggression. In particular, the study seeks to identify the circumstances in which women are most like men in how they express aggression.





Regulatory Policies and Legal Controls
SOCIAL, PREVENTION AND HEALTH POLICY RESEARCH DEPARTMENT

DR. LOUIS GLIKSMAN, HEAD

The Regulatory Policies and Legal Controls Section assesses the impact of policy and legal control initiatives and conducts research on potential policy options for various levels of government. We have implemented or completed a number of significant projects this year. These projects are largely funded from external sources, totalling about \$15 million dollars, and will continue for the next few years.

Antisocial Behaviour, Alcohol and the Automobile

Dr. Reg Smart and Dr. Bob Mann received funding from the Networks of Centres of Excellence program to support their work on drunk driving and road rage. One aspect of this work is a comprehensive analysis of several impaired-driving policy initiatives in Canadian provinces. They have recently assessed the impact of Ontario's Administrative Drivers License Suspension law. They found that, since this law was introduced, there has been a 17 per cent reduction in the proportion of fatally injured drivers with a blood alcohol content over the legal limit.

As well, in a comprehensive review of the literature on road rage, they found that, although scientific literature does not yet support claims of an epidemic of road rage in modern society, some findings suggest that road rage may be an important cause of injuries and deaths on our highways.

Lowering Blood Alcohol Content Limits for Driving

Dr. Mann, Dr. Scott Macdonald and Gina Stoduto have found that every jurisdiction that has introduced or lowered a legal blood alcohol content limit for driving saw a reduction in collisions, injuries and fatalities. Recent studies consistently indicate that a lowered legal limit can be associated with a lasting reduction in collision fatalities. Variations in the impact of reduced legal limits may be due to such factors as levels of awareness and enforcement of the law.

Collaborative World Health Organization Study on Alcohol and Injuries

Drs. Macdonald and Norman Giesbrecht are the Canadian investigators of a world-wide, multi-site comparison study, co-ordinated by the World Health Organization, looking into the relationship between alcohol and injuries in hospital emergency-room departments. The intent of the study is to use a common methodology and to draw comparisons of the relationship across countries.



Driving Records of Clients in Treatment for Alcohol, Cocaine or Cannabis Use

Dr. Macdonald has received funding from the Canadian Institute of Health Research for this study. Using data from client records and traffic violations, the study is looking at the relationship between traffic violations and people in treatment for alcohol, cocaine or cannabis use to determine if this group is more prone to traffic problems. The data collection phase has been completed.

Interdisciplinary Health Research Teams Illicit Opioid Addiction Study

Drs. Benedikt Fischer and Jürgen Rehm and their colleagues have begun three of four of the project components of this national multi-site site study that is funded by the Canadian Institute of Health Research. These include a multi-site cohort study with untreated opioid users, meta-analysis on opioid pharmacotherapy treatments, and an animal studies program. The study is being conducted in a number of cities in Canada, and will use multiple, interrelated disciplines to investigate the appropriateness of a variety of opioid treatment options.

North American Opioid Medications Initiative

The purpose of this study is to determine the extent to which non-conventional forms of opioid-assisted therapy may be more successful than conventional oral methadone therapy in recruiting, retaining, and benefiting chronic, opioid-dependent people who use injection drugs. Drs. Fischer and Rehm are part of a national team that have recently received funds from the CIHR to begin this first study its kind in North America. The study is scheduled to begin this year and to take place in three Canadian cities.

Drug Treatment Courts in Toronto

Dr. Louis Gliksman and Brenda Newton-Taylor have received funding for 4.5 years from the Department of Justice (National Crime Prevention Centre) to evaluate the impact of drug courts in Toronto. The Drug Treatment Court (DTC) offers a new approach to repeat offenders based on the notion of restorative justice. This approach also allows for a unique opportunity for the criminal justice system and treatment agencies to collaborate, and to actively engage in partnerships with community agencies, services and organizations. The study has resulted in a number of sub-projects within the framework of the overall evaluation:

- Using both qualitative and quantitative data, we are investigating the unique needs and issues of female DTC clients, involving women from expelled, graduate and comparison groups, as well as key court members (judge, Crown, duty council, court liaison, therapists).
- We are conducting a summary of drug court related literature, focusing on international comparisons, and research/evaluation issues.
- With DTC judicial collaboration, we will be conducting a qualitative examination of drug related sentencing alternatives distributed to a national sample of justices involved with addicted felons.

Municipal Alcohol Policy and Aboriginal Communities

Dr. Gliksman, Ron Douglas, Margaret Rylett and Claire Narbonne-Fortin have been adapting the Municipal Alcohol Policy approach to be culturally appropriate for First Nations Communities. This adaptation covers three potential environments where alcohol is used and it has been implemented, in part, in a number of communities as a demonstration project. We will use the findings from the demonstration project to develop a research proposal for expanding Community Alcohol Harm Reduction Policy development to other First Nation communities in Ontario and Canada.

Alcohol Policy Developments in the U.S.

Drs. Thomas Greenfield and Norman Giesbrecht have been working on a project, funded by the Robert Wood Johnson Foundation, that focuses on American policy developments with regard to alcohol advertising, pricing and institutional change and the roles of alcohol industry, public opinion, research and political change in their outcome. This study will inform the general public and policy-makers about the factors that contribute to effective, sustainable alcohol policies in the American context.

Canadian Alcohol Policy Project

In this project, funded by the National Health Research and Development Program, Health Canada, Dr. Giesbrecht has examined several Canadian federal and provincial developments in alcohol policy, including privatization trends in alcohol retailing at the provincial level. At the national level, we investigated the effects of changes in trade, smuggling, proposed warning labels on alcohol bottles, intoxication as an excuse for violence and deregulation of alcohol advertising controls as factors that may have aided or hindered the development of these policies.

Canadian-Nordic Alcohol Policy Project

In this ongoing project, funded by a number of Scandinavian agencies, Drs. Giesbrecht and Thor Norstrom are conducting a study that focuses on trends and patterns in access to alcohol and alcohol policy in Canada and the provinces since 1950. By studying changes in access, per capita consumption and drinking-related damage using time series analysis and other methods, they hope to draw out implications for alcohol policies in the Nordic countries.



Social Factors and Prevention Interventions

SOCIAL, PREVENTION AND HEALTH POLICY RESEARCH DEPARTMENT

DR. KATHRYN GRAHAM, HEAD

Research in the Social Factors and Prevention Interventions Section is directed toward identifying environmental (e.g., social, physical, cultural) and individual (e.g., personality, predisposition, risks and protection) factors that are associated with mental health and substance use problems. We then use this knowledge to develop and evaluate research-driven interventions to reduce the occurrence and severity of such problems.

At present, work in the section focuses on: social factors associated with aggression and violence, including alcohol-related aggression; alcohol, gender and aggression; theoretical constructs linking different forms of aggression; school-based and workplace-based prevention programs; research on the relationship between healthy psychosocial development and childhood social factors including poverty, parenting and school culture and environment; the evaluation of early intervention programs for at-risk youth; and research and evaluation on the factors associated with preventing and treating problem gambling.

The following are highlights of current initiatives.



Reducing Aggression and Injury in Bars

Drinking in licensed premises is often associated with aggressive behaviour and injury. Our investigators are leading an international project funded by the U.S. National Institute on Alcohol Abuse and Alcoholism (NIAAA) to evaluate the impact of the *Safer Bars* program on reducing aggression and injury related to drinking in licensed premises. During Phase 1 of the project, conducted during 2000/2001, we completed 800 nights of observations in large-capacity bars in Toronto. This allowed us to develop a baseline measure of the frequency and severity of aggressive incidents.

Phase 2, completed in 2001/2002, involved implementing the *Safer Bars* program in up to 26 randomly selected bars and clubs in Toronto and five bars selected for early participation. A total of 522 bar staff and managers in 23 bars and clubs in Toronto participated in the training program.

The overall response to the program was extremely positive: 98 per cent of respondents who completed the feedback questionnaire indicated that they would recommend the training to others. Significant positive changes were evident on 31 of 32 pre-post training knowledge/attitude questions. Participants also gave high ratings on different aspects of the training and of the trainers. The majority of participants said they would change how they work as a result of the program.

Strengthening Families

Children whose parents have substance use problems are at high risk for a number of problems. In partnership with the University of Buffalo and funded by the NIAAA, our investigators continue to evaluate the Strengthening Families program. The primary objective of the program is to prevent the onset and progression of alcohol and other drug use problems among children whose parents have alcohol problems. This five-year project, now entering its third year, will involve approximately 720 families in which at least one parent was previously in treatment for an alcohol problem.

Currently, five alcohol/drug treatment facilities in Ontario are collaborating on the project: Addiction Services for York Region, Simcoe Outreach Services, the Jean Tweed Centre, St. Mary's Counselling Services, and Alcohol and Drug Services of Thames Valley. Over 150 Ontario families have participated in the program, and retention rates have been very high (in excess of 95 per cent), an indication that families are enjoying the activities.

Preliminary findings from the study were presented in at a meeting of the Society for Prevention Research in June 2002.

Fairness and the Human Spirit at Work

CAMH has been a leading partner with Health Canada over the last 16 years in a research, development and evaluation program devoted to promoting mental health and preventing substance use problems in the workplace. Our ongoing projects focus on the role of interpersonal fairness in the employment relationship and how this affects mental health.

Fairness has been isolated as a powerful influence on mental health and a key mediator of how stress affects health in general. CAMH is the virtual hub of a network that involves hundreds of workplace partners, including the National Quality Institute, the Canadian Business and Labour Centre, the Conference Board of Canada and a consortium of largely university-based Centres for Health Promotion.

To address the issue of stress and fairness in the workplace, researchers from CAMH and the consortium have successfully advanced an instrument called the ssos (the Stress Satisfaction Offset Score) as a means of assessing the extent to which workplace environments are health- or harm-promoting. In addition, we are developing several promising interventions that attempt to redress the balance between satisfaction and stress in troubled workplaces. The ability to balance stress and satisfaction is being used as a criterion for managerial performance in at least one major public utility with which we have been working.

Understanding and Preventing Problem Gambling

As gambling opportunities increase, so does the incidence of problem gambling. To better understand how gambling problems develop, our investigators have completed a study of people who win at gambling and how winning affects the development of problem gambling. Our findings indicate that early wins, along with impulsivity and stressful life experiences, play a role in the development of problem gambling. In addition, people who became problem gamblers tended to have a poorer understanding of random events than those who were not problem gamblers and were more likely than non-problem gamblers to rely on escape or avoidance as a method of coping with problems.

Ongoing work in the gambling area also includes evaluating a curriculum (eight lesson plans and a CD-ROM) developed for Ontario schools for preventing gambling problems. The program addresses two main sources of vulnerability: a lack of knowledge about the nature of random events (e.g., the erroneous belief that you can beat the odds); and the inability to cope with stress. The evaluation involves classes randomly selected to receive the curriculum.



DR. BRENDA TONER, HEAD

Women's Mental Health and Addiction
SOCIAL, PREVENTION AND HEALTH POLICY RESEARCH DEPARTMENT

The Women's Mental Health and Addiction Research Section is dedicated to developing health care that is more responsive to the needs of women. We focus on social, psychological and biological factors to further our understanding of the origin, expression, prevention and treatment of mental health problems and addictions in women. We seek partnerships with a diversity of women to conduct research that will be helpful to all women with mental health and addiction issues.

The section continues to focus on multidisciplinary research collaboration at international and local levels. This year, we strengthened our links to the Clinical Division at CAMH by formally integrating into our section Drs. Nili Benazon and Noreen Stuckless, who are research scientists in the Society, Women and Health Program. The following highlights represent selections of our ongoing and new initiatives.

FUNCTIONAL GASTROINTESTINAL DISORDERS IN WOMEN

Multicentre Trial of Functional Bowel Disorders

The Women's Mental Health and Addiction Research Section has completed recruitment for a study by the United States National Institute of Health for a multicentre trial of functional bowel disorders. We are now in the data analysis phase of the study.

This ongoing study is a unique collaboration between mental health professionals and gastroenterologists from the University of Toronto and the University of North Carolina. We hope to improve understanding and treatment of these chronic and debilitating illnesses that are mainly diagnosed in women.

This study is the first to take a holistic view of these disorders, assessing both the biological and psychosocial impact of cognitive-behavioural therapy versus antidepressant medication. Several papers, abstracts and presentations have been produced from this rich database over the past four years. We anticipate several more papers to be submitted for publication over the next several months.

GENDER ROLE SOCIALIZATION

Development of Gender Role Scale for Women

Gender role socialization refers to the internalization of prescribed gender role messages for women as depicted by multiple sources in society. Theoretical literature suggests that many mental health problems experienced by women are influenced by socialization into the female gender role. We do not yet have a validated tool that measures gender role socialization.

Our group continues working to develop such a tool — a scale to reflect the diversity of women's experience in this area. This scale will serve as a predictive and outcome measure in feminist-informed treatment interventions for women.

We have recently received funding from the Social Sciences and Humanities Research Council of Canada to support this ongoing work for the next three years.

Gender Role Messages for Women: An Intervention

Feminist researchers and clinicians agree on the need to develop interventions that expose and challenge gender role messages for women. However, no existing interventions provide a systematic and detailed account of possible themes and sessions for group or individual therapy with women. As well, very little work has been devoted to empirically testing the efficacy of feminist-informed therapies.



Our group developed an intervention that brings women together across diagnostic categories and encourages women, in a supportive and normalizing shared environment, to openly explore how gender role messages may have affected their sense of well-being. Our group continues to test the efficacy of this approach against more traditional forms of therapy. This project is a collaboration between feminist therapists and researchers in the Society, Women and Health Program and our section.

We have recently written a prospectus for this work, called *Exposing and Challenging Gender Role Messages for Women: Theoretical, Empirical and Clinical Perspectives*. We are currently looking for a publisher for this work.

Complex Post-traumatic Stress Disorder

Dr. Linda McLean received an Eli Lilly Canada Fellowship in Women's Mental Health Research. This fellowship will help facilitate a program of research called "The development of a complex post-traumatic stress disorder, dissociation, somatization, childhood trauma, and alexithymia in an outpatient sample of women."

The objective of this research will be to examine the strength of the relationship between the diagnosis of complex post-traumatic stress disorder, “early” (i.e., 12 years of age or less) childhood trauma variables, dissociation, somatization and alexithymia. We hope the findings will advance the understanding of the course, expression, prevention and clinical implications of such childhood experience(s), and inform treatment.

Trichotillomania

Using qualitative methodologies, Josee Casati has played a leadership role in identifying themes involving women's experiences with trichotillomania or compulsive hair pulling. Specifically, the purpose of this study was to better understand how women with trichotillomania conceptualized their condition, what their worries and concerns were and what feelings were associated with their hair pulling.

The study identified ten major themes prominent for women with trichotillomania, including embarrassment/shame, isolation, fear/guilt, anger/frustration, humiliation/pain, body image, lack of control, self-disclosure, lack of information from the medical community and precipitating triggers.

Findings from this study point to the importance of acknowledging and addressing psychosocial concerns for women with trichotillomania. Increasing our understanding of psychosocial issues underlying compulsive hair-pulling will contribute to improved treatment strategies for women.

Immigrant Women and Women of Colour

Dr. Alisha Ali, who has worked at CAMH as a research scientist, has accepted a position as Assistant Professor in the Department of Applied Psychology at New York University. We are also pleased to state that Alisha will continue to collaborate with our important work focusing on immigrant women and women of colour and with our ongoing research on gender role socialization.

Life Role Changes that Contribute to Well-Being among Immigrant Chinese Women

Taryn Tang leads this program of research, now in its second year, that examines Chinese immigrant women's negotiation of change in their lives and the types of mechanisms and processes that contribute to adjustment in Canada.

Anticipating and meeting the needs of a healthy population in a given society is a preventative measure that is a more cost-effective long-term solution than retrospectively maintaining the health demands of an ill population. This research can inform the investment practice of governments: we will compare different models of coping and support to develop an understanding of factors that guard against mental illness and promote mental health.

Training and Education

The Women's Mental Health and Addiction Research Section is also active in professional training, media presentations and public forums with a view of influencing the provision of care to women locally and internationally. In particular, we have been active in teaching undergraduate, graduate and post-graduate levels in psychiatry and psychology. We encourage electives, fellowships and post-doctoral positions in Women's Mental Health and Addiction, and are particularly interested in helping to develop academic careers in women's health. To increase communication among all staff and students interested in women's health issues, we developed and maintain the city-wide Women's Mental Health Interest Group in Toronto, a group that arranges monthly presentations on issues across the spectrum of women's health.

Honours, Appointments and Awards

Adlaf, Edward. Received Robin Badgely Award for Excellence in Teaching, Department of Health Sciences, University of Toronto.

Ali, Alisha. Appointed Assistant Professor, Department of Psychiatry, University of Toronto.

Arnold, Paul. Received award for Best Resident Poster Presentation at the Canadian Academy of Child Psychiatry Conference.

Atkinson, Leslie; Goldberg, Susan; Levitan, Robert; Masellis, Mario; Basile, Vincenzo; Macciardi, Fabio & Leung, Eman. Received CAMH Research in Psychiatry Award for *HPA – Axis Candidate Genes in Infant Cortisol Stress Response*.

Atkinson, Leslie. Appointed Member, Psychosocial, Sociocultural and Behavioural Determinants of Health Grants Committee, Canadian Institutes of Health Research; Appointed Co-chair, National Expert Advisory Committee on Centres of Excellence for Children's Wellbeing.

Bagby, Michael. Received CAMH Research in Psychiatry Award for *Examining Response Style in Analogue and "Real World" Samples with the Revised NEO PI*; Appointed to editorial board of *European Journal of Personality*; Appointed to editorial board of the *Journal of Personality Assessment*.

Barbaree, Howard. Received CAMH Research in Psychiatry Award for *Evaluating the Accuracy of Actuarial Predictions of Sexual Offense Recidivism Adjusted Using Clinical Judgement*.

Beitchman, Joseph. Article "A Review of the Long-Term Effects of Child Sexual Abuse," selected as a "citation classic," a highly cited paper in the field of Social Sciences by ISI's Essential Science Indicators.

Beiser, Morton. Appointed Director of the Toronto Centre of Excellence for Research on Immigration and Settlement (CERIS) for a second term; Appointed Chair of the Immigration Medical Advisory Board of Citizenship and Immigration Canada; Appointed to the External Advisory Committee, National Longitudinal Study of Immigrants, Citizenship and Immigration Canada.

Benazon, Nili. Appointed Assistant Professor, Department of Psychiatry, University of Toronto; Received Career Development Travel Award, Anxiety Disorders Association of America.

Bush, David. Awarded the Certificate in Teaching in Biomedical Science, Institute of Medical Science, University of Toronto.

Buckley, Leslie. Elected President of the Professional Association of Interns and Residents of Ontario (PAIRO).

Cheung, Amy. (and colleagues) Awarded Best Paper, Canadian Psychiatric Association.

Chow, Eva. Appointed Member, Research Committee, Ontario Mental Health Foundation.

Cunningham, John. Promoted to Associate Professor, Department of Psychology, University of Toronto.

Daskalakis, Jeff. Received 2001 Mary Early Fellow, awarded to the highest ranked grant application of the Canadian Psychiatric Research Foundation.

Devins, Gerald. Re-appointed Chairperson of the Canadian Institutes of Health Research Psychosocial, Sociocultural and Behavioural Determinants of Health Committee.

Fan, Nancy. Received Resident Award, Canadian Academy of Geriatric Psychiatry.

Farvolden, Peter. Received CAMH Research in Psychiatry Award for *Childhood Adversity, Adult Attachment Style and Interpersonal Functioning in Depression*.

Fischer, Benedikt & Rehm, Jürgen. Received CAMH Research in Psychiatry Award for *Illicit Opiates, Co-morbidity and Self-Medication*.

Giesbrecht, Norman. Appointed Chair, Alcohol and Tobacco and Other Drug Section, American Public Health Association.

Gliksman, Louis. Appointed to board of McGill International Centre of Gambling.

Goering, Paula. Received the C.M. Hinks Award, Canadian Mental Health Association; Received Leighton Award in Psychiatric Epidemiology, Canadian Academy for Psychiatric Epidemiology and Canadian Psychiatric Association.

Hathaway, Andrew. Received Canadian Policy Research Award for dissertation on harm reduction.

Jacobson, Nora. Appointed to Assistant Professor, Department of Psychiatry, University of Toronto.

Khanlou, Nazilla. Appointed to lead the Health Domain of the Toronto Joint Centre of Excellence for Research on Immigration and Settlement.

Kapur, Shitij. Received Young Explorers Prize, Canadian Institute for Advanced Research, recognizing distinguished researchers aged 40 and under currently working in Canada.

Kish, Stephen. Received Addiction Award, Canadian Psychiatric Research Foundation.

Lalumiere, Martin. Appointed to editorial board, *Archives of Sexual Behavior*; Appointed to editorial board, *Sexual Abuse*; Received Kurt Freund Memorial Research Prize.

Macciardi, Fabio. Received Joanne Murphy Professorship of Behavioural Neuroscience, Centred on Hope Campaign.

Macdonald, Scott. Appointed Associate Professor, Department of Psychology, University of Western Ontario; Appointed Senior Associate, Centre for Applied Sustainability, York University.

McIntyre, Roger. Received The Council of Psychiatric Continuing Education/Canadian Psychiatric Association Award for the most outstanding continuing education activity in psychiatry in Canada for continuing education planners affiliated with a medical school.

McLean, Linda. Dissertation nominated for the Frida Fromm-Reichmann Research Award for contribution to psychoanalytic theory and clinical practice; Dissertation nominated for the American Psychological Foundation/Council of Graduate Departments of Psychology Graduate Research in Psychology Award.

McNeely, Heather. Received CAMH Research in Psychiatry Award for *Brain Wave Activity in Major Depression*; Appointed Assistant Professor, Department of Psychiatry, University of Toronto.

Mann, Robert. Served as Chair, National Institute on Alcohol Abuse and Alcoholism Special Panel on Alcohol Epidemiology and Prevention (July 2001) and Co-Chair, Special Emphasis Panel (October 2001); Served on the International Scientific Committee, 16th International Conference on Alcohol, Drugs and Traffic Safety.

Miller, Fiona: Successfully defended PhD dissertation; Appointed to Department of Psychiatry, Hospital for Sick Children.

Nobrega, Jose. Received CAMH Research in Psychiatry Award for *Brain Mechanisms in Ethanol Sensitization*.

Nussbaum, David. Appointed to the Practice Analysis Task Force to update specifications underlying the Examination for Professional Practice in Psychology, Association of State and Provincial Psychology Board.

O'Dowd, Brian. Promoted to Professor, Department of Pharmacology, University of Toronto.

Rahman, Shafiq. Received CAMH Research in Psychiatry Award for *Neurochemical Mechanisms Underlying Nicotine Addiction: In Vivo Microdialysis Study*.

Rotzinger, Susan. Received CAMH Research in Psychiatry Award for *Neurochemical Effects of Microinjections of T-CAP, a Novel, CRF-like Peptide*; Cross-appointed as Adjunct Professor, Department of Zoology, University of Toronto; Cross-appointed as Assistant Professor, Department of Psychology, University of Toronto.

Rummens, Joanna. Appointed to Advisory Committee planning the Canadian Ethnic Diversity Survey, Statistics Canada and Canadian Heritage.

Sanford, Mark & Levac, Anne Marie. Received CAMH Research in Psychiatry Award for *Child Resiliency Screen for Families Experiencing Substance Abuse and Psychiatric Disorders*.

Seeman, Mary. Received Lifetime Membership Status, Ontario Psychiatric Association; Gold Award for Advancement of Research, Canadian Psychiatric Association.

Selby, Peter. Received CAMH Research in Psychiatry Award for *Tobacco Intervention Programmes for Patients with Schizophrenia: A Needs Assessment*.

Sellers, Edward. Received Senior Investigator Award, Canadian Society for Clinical Pharmacology.

Seto, Michael. Chaired committee that produced a Practice Standards and Guidelines document for members of the Association for the Treatment of Sexual Abusers; Appointed to editorial board, *Archives of Sexual Behavior*.

Shain, Martin. Appointed Chair of the Scientific Advisory Committee to the Business and Economic Roundtable on Addiction and Mental Health.

Skilling, Tracy. Appointed Assistant Professor, Department of Psychology, University of Toronto; Received Clinical Investigators Training Program Award, The Mental Health Centre, Penetanguishene through the Department of Psychiatry, McMaster University; Received CAMH Research in Psychiatry Award for *Clinical Versus Actuarial Estimates of Risk among Young Offenders and Their Relationship to Recidivism*.

Strike, Carol. Appointed to Assistant Professor, Department of Psychiatry, University of Toronto; Received CAMH Research in Psychiatry Award for *Profile of Ontario Methadone Recipients and Providers*.

Stuckless, Noreen. Appointed board member, North York Women's Centre.

Toner, Brenda. Nominated for the Paul E. Garfinkel Award for Excellence in Fellowship Supervision, Department of Psychiatry, University of Toronto; Appointed Member, Promotions Committee, University of Toronto.

Tyndale, Rachel. Received William's Memorial Lecture Award, Department of Pharmacology & Therapeutics, Tampa, Florida; Appointed to the Scientific Advisory Committee, Fundamental Neuroscience Network, University of Toronto; Appointed to the grant review panel, Tobacco-Related Disease Research Program; Appointed to the Scientific Program Committee, 7th International meeting of the International Society for the Study of Xenobiotics; Appointed to the Scientific Committee, X World Conference on Lung Cancer; Planned and chaired the scientific session for Pacific Rim Association for Clinical Pharmacology; Appointed to Pharmacology and Toxicology Review Panel B for operating grants, Canadian Institutes of Health Research.

Vaccarino, Franco. Received 2001 Heinz Lehman Award, Senior Award for outstanding contributions to Neuropsychopharmacology, Canadian College of Neuropsychopharmacology.

Van Tol, Hubert. Promoted to Full Professor, Department of Psychiatry, Pharmacology and Institute of Medical Sciences, University of Toronto.

Warner, Jessica. Appointed to the Executive Council of the Alcohol and Temperance Group.

Wong, Albert. Promoted to Assistant Professor, Department of Psychiatry, University of Toronto; Received Julius, Dorota and Sofia (Zosia) First Memorial Prize in Neuropsychopharmacology, University of Toronto.

Zack, Martin & Fletcher, Paul. Received CAMH Research in Psychiatry Award for *Chronic Use of MDMA and Inhibitory Control of Behaviour – II: Roles of Concurrent Marijuana and Other Drug Use.*

Zipursky, Robert. Promoted to Professor of Psychiatry, University of Toronto.

Grants and Contracts

Adlaf, E. & Turner, N. *Schools, Students and Adolescent Gambling in Ontario*. Ontario Problem Gambling Research Centre

Allison, K., Adlaf, E., Dwyer, J. & Goodman, J. *Physical Activity Promotion among Youth*. Heart and Stroke Foundation of Ontario

Arnold, P. *Investigation of Serotonin-Dopamine Interaction in Obsessive-Compulsive Disorder: An Innovative Strategy Combining Genetics and Neuroimaging*. Ontario Mental Health Foundation

Ashley, M.J., Cohen, J. & Ferrence, R. *On the Front Line: Exploring the Expanding Roles of Pharmacists in Smoking Cessation*. National Cancer Institute of Canada

Bagby, R.M. *Patient Dimensions as Predictors of Response, Relapse and Recurrence following Cognitive-Behavioural Therapy, Interpersonal Psychotherapy and Pharmacotherapy Treatment of Patients with Major Depression* (operating grant). Ontario Mental Health Foundation

Bagby, R.M. *Personality and Major Depression: Predicting Treatment Outcome and Neuropsychological Status*. National Institutes of Health

Bagby, R.M. *Personality as a Predictor of Relapse and Recurrence of Major Depression*. National Institutes of Health

Bagby, R.M. & Christi, C. *Patient Dimensions as Predictors of Response, Relapse and Recurrence following Cognitive-Behavioural Therapy, Interpersonal Psychotherapy and Pharmacotherapy Treatment of Patients with Major Depression* (personal award). Ontario Mental Health Foundation

Bagby, R.M. & Taylor, G. *Development of a Structured Interview to Assess the Alexithymia Construct*. Social Sciences and Humanities Research Council of Canada

Bagby, R.M., Fervolden, P., Toneatto, T. & Oakman, J. *Personality and Vulnerability in Problem Gambling*. Ontario Problem Gambling Research Centre

Barr, C. & Kennedy, J.L. *Investigation of Genetic Factors in Attention Deficit Hyperactivity Disorder*. Canadian Institutes of Health Research

Barr, C., Kovacs, M. & Kennedy, J.L. *Risk Factors in Childhood-Onset Depression (Supplement)*. National Institutes of Health

Barr, C., Lovett, M., Beitchman, J., Humphries, T., Tannock, R. & Macciardi, F. *Genetics of Reading Disabilities*. Canadian Institutes of Health Research

Bassett, A., Brustowicz, L., Homer, W., Husted, J. & Chow, E. *Localizing Genes for Familial Schizophrenia*. Canadian Institutes of Health Research

Bassett, A.S., Chow, E., Weksberg, R., Zipursky, R., Bryustowicz, L. & Siu, S. *A Screening Strategy for a Genetic Subtype of Schizophrenia*. Canadian Institutes of Health Research

Bassett, A.S., Husted, J. & Chow, E. *Identifying Predictive Factors for Familial Schizophrenia*. Bill Jeffries Schizophrenia Endowment Fund

Beiser, M. *Education Media Project Immigration and Refugee Issues Computer Assisted Learning (EMPIRICAL)*. Citizenship and Immigration Canada

Beiser, M. *Online Development Project*. Citizenship and Immigration Canada

Beiser, M. *Society, Culture and the Health of Canadians — Multicultural Meanings of Social Support among Immigrants and Refugees* (sub-grant with University of Alberta). Social Sciences and Humanities Research Council of Canada

Beiser, M. & Kaspar, V. *New Canadian Children and Youth Study*. Canadian Institutes of Health Research

Beiser, M. & Noh, S. *A Community in Distress: Mental Health in the Tamil Community*. Canadian Institutes of Health Research

Beiser, M. & Simich, L. *Alone in Canada: A Self-Help Guide for Single Newcomers — translation into seven languages*. Citizenship and Immigration Canada

Beiser, M., Killbride, K., Amrhein, C. & Lanphier, M. *Joint Centre of Excellence for Research on Immigration and Settlement — Toronto*. Social Sciences and Humanities Research Council of Canada

Beitchman, J. & Broder, E. *Telepsychiatry for Remote and Rural Ontario*. Ministry of Community and Social Services

Beitchman, J., Johnson, C., Young, A., Atkinson, L., Adlaf, E., Escobar, M. & Vohra, S. *The Ottawa Language Study: The Moderating Effects of Transitional Age Variables on Psychological Outcomes: A 20 Year Follow-up Study*. Canadian Institutes of Health Research

Bishop, S.R., Anderson, N.D., Abbey, S.E., Devins, G.M., Segal, Z.V. & Lau, M.A. *Toward a Program of Research in Mindfulness-Based Stress Reduction: Validating and Specifying the Construct of Mindfulness and the Development of Self-Report Measure*. Canadian Institutes of Health Research

Blanchard, R., Christensen, B.K. & Dickey, R. *Cognitive Functioning in Pedophiles*. Social Sciences and Humanities Research Council of Canada

Boydell, K. & Trainor, J. *CMHEI Project: A Longitudinal Evaluation of Family Initiatives in Ontario*. Ontario Mental Health Foundation

Brown, G., Swinson, R., Antony, M. & Katzman, M. *Brain Function in Panic Disorder: PET Studies*. Canadian Institutes of Health Research

Brzustowicz, L., Bassett, A. & Cox Matisse, T. *Molecular Genetics of a Schizophrenia Locus on 1q21-22*. National Institutes of Health

Busto, U. & Naranjo, C. *The Role of Brain Reward System in Depression*. Ontario Mental Health Foundation

Busto, U., Naranjo, C., Mayberg, H. & Cardenas, L. *Brain Reward System, Depression, and Nicotine Dependence*. National Institute on Drug Abuse

- Busto, U., Streiner, D., Herrmann, N. & Sproule, B.** *The Comparative Pharmacological Effects of Temazepam, Diphenhydramine, and Valerian in Elderly Subjects.* Canadian Institutes of Health Research
- Calzavara, L., Strike, C., Millson, M., Major, C., Myers, T., Fischer, B. & Remis, R.** *Rapid Assessment of Injection Drug Use in Peel Region.* Region of Peel Public Health Department
- Castel, S., Kennedy, S.H., & Rush, B.** *The Assessment of the Role of Concurrent Substance Use and Mental Health Disorders in the Utilization Abuse and Community Services and Associated Outcomes.* Canadian Institutes of Health Research
- Christensen, B., Zipursky, R. & Kapur, S.** *Schizophrenia as a Neurodevelopmental Disorder: Selective Dorsal Pathway Impairment.* Canadian Psychiatric Research Foundation
- Cohen, J., Abernathy, T., Adlaf, E., Ashley, M.J. & Ferrence, R.** *Support for Tobacco Control Policy Measures: Multi-Level Analysis.* Social Sciences and Humanities Research Council of Canada, Canadian Tobacco Research Initiative Planning Grant
- Cohen, J., Ashley, M.J., Ferrence, R. & Steward, D.** *Institutional Addiction to Tobacco: Defining Links between the Tobacco Industry and Academic and Health Institutes.* National Cancer Institute of Canada
- Cohen, J., Brown, S., Campbell, S., Adlaf, E., D'Avernas, J., Ferrence, R. & Garcia, J.** *Tobacco Control Policies: A Program of Research.* Canadian Tobacco Control Research Initiative, National Cancer Institute of Canada
- Collins, J., Skinner, W. & Toneatto, T.** *Beyond Assessment: The Impact of Comorbidity of Pathological Gambling, Psychiatric Disorders and Substance Use Disorders on Treatment Course and Outcomes.* Ontario Problem Gambling Research Centre
- Corrigall, W.** *Cholinergic and Opiate Mechanisms in Drug Reinforcement.* National Institute on Drug Abuse
- Corrigall, W.** *Preclinical Evaluation of Medications for Smoking Cessation.* Addiction Therapies, Inc.
- Corrigall, W., Zack, M. & Eissenberg, T.** *Adolescent Smoking: Trajectory to Nicotine Dependence.* Robert Wood Johnson Foundation
- Cunningham, J.A.** *The Impact of Self-Help Materials for Problem Drinkers: Population Studies.* Canadian Institutes of Health Research
- Cunningham, J.A., Koski-Jannes, A. & Wild, T.C.** *Treating Alcohol Problems with Self-Help Materials.* National Institute on Alcohol Abuse and Alcoholism
- DaSilva, J.N.** *Development of New Dopamine D1 Agonist Radioligands for Studying D1 Receptors with PET.* Canadian Institutes of Health Research
- DaSilva, J.N.** *Rolipram as a Probe for PDE4 Activity — Part V: In Vivo Rat Studies on the Serotonin, Histamine, Glutamate, Dopamine and Norepinephrine Systems.* Eli Lilly Canada Inc.
- DaSilva, J.N.** *Rolipram as a Probe for PDE4 Activity: Part IV — Human PET Validation Studies.* Eli Lilly Canada Inc.
- Daskalakis, Z.** *A Study of Intracortical Inhibition and Facilitation in Schizophrenia using Transcranial Magnetic Stimulation.* Ontario Mental Health Foundation
- Daskalakis, Z., Kapur, S., Christensen, B. & Chen, R.** *A Study of Cortical Inhibition in Schizophrenia Using Transcranial Magnetic Stimulation.* Canadian Psychiatric Research Foundation
- Devins, G. & Beiser, M.** *Cultural Syndromes, Coping, and the Psychosocial Impact of Illness Intrusiveness in Cancer.* Canadian Institutes of Health Research
- Devins, G.M.** *Quality of Life and Psychosocial Impact of Chronic Disease (Senior Scientist Award).* Canadian Institutes of Health Research
- Dewa, C.** *Career Scientist Award.* Ontario Ministry of Health and Long-Term Care
- Dewa, C., Goering, P. & Lin, E.** *Depression in the Workplace: Assessing Treatment and Predicting Disability.* Ontario Round Table on Appropriate Prescribing
- Drossman, D.A., Toner, B.B., Whitehead, W. & Diamant, N.E.** *Multicenter Trial of Functional Bowel Disorders.* National Institutes of Health
- Dunn, E.** *Analysis of Doxylamine in Rabbit Plasma Samples.* Delux Therapeutics
- Dunn, E.** *Analysis of Fentanyl in Rabbit Plasma Samples.* Delex Therapeutics
- Durbin, J., Rogers, J., Macfarlane, D., Cochrane, J. & Goering, P.** *Best Practices in Mental Health Systems Integration.* Ontario Mental Health Foundation
- Erickson, P., Harrison, L. & Adlaf, E.** *A Cross National Study of the Youth Drugs Violence Nexus.* National Institute on Drug Abuse
- Ferrence, R., Ashley, M.J., Bull, S., Cohen, J., Lovato, C. & Potvin, L.** *A National Study on Environmental Tobacco Smoke in the Home.* National Cancer Institute of Canada
- Ferrence, R., Cohen, J., Ashley, M.J., Selby, P., Tremblay, P. & Broadway, T.** *Protecting Children's Health: The Role of Primary Care Physicians Addressing Environmental Tobacco Smoke (ETS) in Home Environments.* The Hospital for Sick Children Foundation
- Ferrence, R., Cohen, J., Kaufman, P., Perkins, N., Perley, M. & Poland, B.** *Smoking in Outdoor Public Places: A Study of Socio-Spatial Relationships.* Canadian Tobacco Control Research Initiative, National Cancer Institute of Canada
- Ferrence, R., Rootman, I., Ashley, M.J., Brown, K.S., Cohen, J. & McDonald, S.T.** *Plans for Enhanced Surveillance, Evaluation and Research (CAMH sub-grant with University of Toronto).* Ontario Ministry of Health and Long-Term Care

- Ferrence, R., Rootman, I., Ashley, M.J., Brown, K.S., Cohen, J., McDonald, P. & Stephens, T.** *Ontario Tobacco Research Unit* (sub-grant with University of Toronto). Ontario Ministry of Health and Long-Term Care
- Fischer, B.** *Illicit Opiate Addiction (IHRT) — Training Grant*. Canadian Institutes of Health Research-Institute of Neurosciences, Mental Health and Addiction
- Fischer, B.** *International Opiate Pharmacotherapy Research and Policy*. Joint Initiative in German and European Studies
- Fischer, B.** *New Investigator Award: Illicit Drug Use, Treatment and Policy*. Canadian Institutes of Health Research
- Fischer, B.** *Over Time Analysis of Injection Drug Use Related Harms and Determinants in Western Jurisdictions*. Connaught Foundation, University of Toronto
- Fischer, B., Brissette, S., Brochu, S., Bruneau, J., El-Guebaly, N., Lauzon, P., Marsh, D., O'Shaughnessy, M., Poulin, C., Rehm, J., Schechter, M., Single, E., Stewart, J., Tyndall, M. & Wild, C.** *Illicit Opiate Addiction Treatment, Research and Policy*. Canadian Institutes of Health Research
- Fletcher, P.** *Career Scientist Award*. Ontario Ministry of Health and Long-Term Care
- Fletcher, P.** *Serotonin-Dopamine Interactions and Reward Related Behaviour*. Canadian Institutes of Health Research
- Fletcher, P.** *The Role of the Ventral Pallidum in Mediating Drug Reinforcement*. Natural Sciences and Engineering Research Council
- Fletcher, P. & Sill, T.L.** *Prefrontal Cortex Monoamines and Behaviour*. Canadian Institutes of Health Research
- Fornazzari, L.** *Early Detection of Mild Cognitive Impairment*. Ontario Ministry of Health and Long-Term Care
- George, S.R. & O'Dowd, B.F.** *Receptors Mediating Drug Dependence*. National Institute on Drug Abuse
- George, S.R. & O'Dowd, B.F.** *Neuropeptide Receptors and Ligands*. Canadian Institutes of Health Research
- George, S.R. & O'Dowd, B.F.** *The Biology of Dopamine and Other Amine Binding Receptors*. Canadian Institutes of Health Research
- George, S.R. & O'Dowd, B.F.** *Identification and Characterization of Novel GPCR Genes*. Merck Frosst Canada Inc.
- Gerald, D. & Beiser, M.** *Gender and Ethnocultural Moderators of Illness-Intrusiveness across the Life Span*. Canadian Institutes of Health Research
- Giesbrecht, N. & Degustis, L.C.** *A Comparative Analysis of the Passage and Failure of DWI Legislation and Regulation in the U.S. and Canada* (sub-grant agreement with Yale University). Robert Wood Johnson Foundation
- Ginovart, N., Kapur, S. & Houle, S.** *Can Dopamine D2 Receptor Upregulation by Antipsychotics Be Avoided by a Different Regimen of Occupancy Kinetics? A Longitudinal [¹¹C]-Raclopride PET Study*. National Alliance for Research on Schizophrenia and Depression
- Ginovart, N., Kapur, S. & Houle, S.** *Imaging Endogenous Dopamine Levels with In Vivo [¹¹C] Raclopride Displacement Studies: Understanding the True Mechanism*. Canadian Institutes of Health Research
- Ginovart, N., Wilson, A.A. & Houle, S.** *In Vivo Characterization of Potential Radioligands for Imaging the Serotonin Transporter: Leads for the Development of In Vivo Strategies to Evaluate Serotonergic Dysfunctions Using Positron Emission Tomography*. Connaught Foundation, University of Toronto
- Goering, P.** *Canadian Health Services Research Foundation Chair Award*. Canadian Institutes of Health Research
- Goering, P.** *Community Mental Health Evaluation Initiative Coordinating Centre*. Ontario Mental Health Foundation
- Goering, P.** *Supervisor for Student Award to Caroline O'Grady*. Social Sciences and Humanities Research Council of Canada
- Goering, P. & Butterill, D.** *Research Transfer Training Program*. Ontario Ministry of Health and Long-Term Care
- Goering, P., Durbin, J., Macfarlane, D., Koegl, C. & Sheldon, T.** *Central South Ontario Community Comprehensive Assessment Program*. Central South Mental Health Implementation Task Force
- Goering, P., Durbin, J., Macfarlane, D., Koegl, C. & Sheldon, T.** *Northwest Ontario Community Comprehensive Assessment Program*. Northwestern Ontario District Health Council
- Goering, P., Durbin, J., Macfarlane, D., Koegl, C. & Sheldon, T.** *Penetanguishene Community Comprehensive Assessment Program*. Penetanguishene Area Mental Health Implementation Task Force
- Goering, P., Durbin, J., Macfarlane, D., Koegl, C. & Sheldon, T.** *Southeast Ontario Community Comprehensive Assessment Program*. Southeastern Ontario Mental Health Implementation Task Force
- Goering, P., Durbin, J., Macfarlane, D., Koegl, C. & Sheldon, T.** *Whitby Community Comprehensive Assessment Program*. Central East Mental Health Implementation Task Force
- Goering, P., Macfarlane, D., Durbin, J., Sheldon, T., Palmer, H. & Koegl, C.** *Community Comprehensive Assessment Project*. Northeastern Implementation Task Force/Champlain Implementation Task Force/Grand River District Health Council
- Goering, P., Macfarlane, D., Shulman, K. & Rodgers, J.** *Mental Health Centre Penetanguishene Admission Assessment Program Review*. Penetanguishene Mental Health Centre

- Graham, K., Osgood, D.W. & Gliksman, L.** *Safer Bars: Evaluating an Intervention to Reduce Barroom Violence*. National Institute on Alcohol Abuse and Alcoholism
- Guttman, M.** *CARE-HD*. National Institutes of Health
- Guttman, M.** *Center of Excellence Award*. National Parkinson Foundation
- Guttman, M.** *Clinical Assistance Program*. Parkinson Society Canada
- Guttman, M.** *PHAROS*. National Institutes of Health
- Guttman, M.** *Study 248: Open Label Remacemide in Huntington's Disease*. AstraZeneca Canada Inc.
- Guttman, M.** *Study 320: Neuroprotective Study in Parkinson's Disease*. Aventis
- Guttman, M.** *Study 321: Neuroprotective Studies in Parkinson's Disease*. Aventis
- Henderson, J.** *Social Sciences and Humanities Research Council Doctoral Fellowship*. Social Sciences and Humanities Research Council of Canada
- Hodgins, D.C., Toneatto, T., Makarchuk, K., Skinner, W. & Vincent, S.** *Minimal Treatment Approaches for Concerned Significant Others of Problem Gamblers*. Ontario Problem Gambling Research Centre
- Houle, S. & Vaccarino, F.** *Functional Imaging Research Network: PET Component*. Canadian Foundation for Innovation and Ontario Innovation Trust
- Husted, J. & Bassett, A.** *Gene-Environment Interaction in Familial Schizophrenia*. National Alliance for Research on Schizophrenia and Depression
- Jain, U., Barton, R., Spence, W. & Lamm, C.** *A Randomized, Double Blind, Cross-Over Comparison of the Safety and Efficacy of Controlled-Release Methylphenidate and Immediate Release Methylphenidate for Attention Deficit Hyperactivity Disorder*. Purdue Pharma
- Jain, U., Turner, N. & Spence, W.** *Special Populations in Gambling: Attention Deficit Hyperactivity Disorder (ADHD) and Pathways to Problem Gambling*. Ontario Problem Gambling Research Centre
- Kapur, S.** *Canada Research Chair (Tier II)*. Canadian Institutes of Health Research
- Kapur, S.** *5-HT_{1A} Receptors in Schizophrenia: A PET Investigation*. EJLB Foundation Scholar Program
- Kapur, S.** *Infrastructure for Translational Research in Therapeutic Neuroscience: Bridging Clinical Findings to Animal Models Using PET Imaging*. Canada Foundation for Innovation
- Kapur, S.** *Infrastructure for Translational Research in Therapeutic Neuroscience: Bridging Clinical Findings to Animal Models Using PET Imaging*. Ontario Innovation Trust
- Kapur, S.** *Seroquel Sustained Release (SR) vs. Immediate Release (IR) PET Study*. AstraZeneca Canada Inc.
- Kapur, S. & Fleming, A.** *Differential Effects of Antipsychotics on Maternal Behaviour*. AstraZeneca Canada Inc.
- Kapur, S. & Remington, G.** *An Open-Label Study Assessing the In-Vivo D₂ Occupancy of IM Olanzapine Depot Using PET Imaging in Patients with Schizophrenia*. Eli Lilly Canada Inc.
- Kapur, S. & Zipursky, R.** *PET Investigations of Endogenous Dopamine and Clinical Response in Schizophrenia*. Canadian Institutes of Health Research
- Kapur, S., Apiquian, R., Ulloa, E., Fresan, A. & Nicolini, H.** *Amoxapine as an Atypical Antipsychotic: A Comparative Study vs. Risperidone*. Stanley Research Foundation
- Kapur, S., Lancot, K., Herrmann, N. & Black, S.E.** *PET Study of 5-HT_{1A} Receptors in Alzheimer's Disease*. Alzheimer's Association
- Kapur, S., McClelland, R.B., Nobrega, J.N. & Rompre, P.P.** *The Pharmacological Basis of Atypical Antipsychotic Activity — A New Hypothesis*. Canadian Institutes of Health Research
- Kapur, S., Seeman, P. & Baker, G.** *Dynamic Aspects of Drug-Receptor Interaction: Implications for Antipsychotic Action*. Stanley Research Foundation
- Kaspar, V.** *Health and Development of Immigrant and Minority Children and Youth*. Canadian Institutes of Health Research
- Kaspar, V. & Noh, S.** *Mental Health of Resettled and Non-Resettled Youth with Lifetime Exposure to War-Related Traumatic Events*. Social Sciences and Humanities Research Council of Canada
- Katz, M. & Devins, G.M.** *A Randomized Controlled Trial of Psychoeducation vs. Standard Care in Oral Cancer Patients*. National Cancer Institute of Canada
- Katzman, D., Zipursky, R., Christensen, B., Young, A. & Mikulis, D.** *Neurobiologic Determinants of Cognitive Outcome in Adolescent-Onset Anorexia Nervosa*. Ontario Mental Health Foundation.
- Keating, D.P., Miller, F.K., Sagar, A., Landy, S., Atkinson, L., Bradley, S. & Wittenberg, J.V.** *Aggression Problems in Young Children: Early Intervention in a Community Based Approach*. Change Foundation
- Kelly, J., Skinner, W. & Turner, N.** *Project Weathervane*. Ontario Ministry of Health and Long-Term Care
- Kennedy, J.L.** *Genetic Studies of Psychosis in Portugal*. National Institutes of Mental Health
- Kennedy, J.L.** *Materials Transfer Agreement*. Psychiatric Genomics Inc.
- Kennedy, J.L. & Macciardi, F.M.** *Strategies for Gene Discovery in Schizophrenia*. Canadian Institutes of Health Research

- Kennedy, S.H., Levitan, R.D. & Srinivasan, J.** *A Double-Blind, Multicentre Extension Trial in Subjects Who Suffer from Major Depressive Disorder with Atypical Features Who Participate in the Placebo and Paroxetine Controlled Study of Org 33062 ER.* Organon Inc.
- Kennedy, S.H., Levitan, R.D. & Srinivasan, J.** *A Double-Blind, Multicentre, Randomized, Placebo-Controlled, Parallel Group Study of Efficacy and Safety of Org 33062 ER and Paroxetine in Subjects Who Suffer from Major Depressive Disorder.* Organon Inc.
- Kennedy, S.H., Mayberg, H.S. & Segal, Z.** *Limbic-Cortical Metabolic Changes as a Final Common Pathway of Depression Remission: A Comparison of Venlafaxine and Cognitive Behavioural Therapy.* Wyeth Ayerst Canada Inc.
- Kennedy, S.H., McIntyre, R.S. & Grigoriadis, S.** *A Parallel Group, Multicentre Flexible Dose Study with a Double-Blind, Randomized, Placebo-Controlled Phase and an Open-Label Phase to Evaluate the Efficacy and Safety of Viagra in Males with Serotonergic Antidepressant Associated Erectile Dysfunction.* Pfizer Inc.
- Kennedy, S.H., McIntyre, R.S., Katzman, M., Schwartz, M. & Srinivasan, J.** *A Multicenter, Picotal, Safety and Efficacy Study of the NeuroCybernetic Prosthesis System in Patients with Depression.* Cyberonics Inc.
- King, G., DeWit, D., LaPorta, J., MacDougall, J., Meyer, K., Miller, L. & Offord, D.** *Predictors of Canadian Children's Mental Health and Competence: A Structural Equation Modelling Approach Using the National Longitudinal Survey of Children and Youth.* National Health Research and Development Program (CIHR)
- Kish, S.J., Guttman, M., Warsh, J., Saint-Cyr, J., Houle, S., Blake, J., Schapiro, C. & Wilson, A.** *PET Neuroimaging Study of the Brain Serotonin Transporter in Parkinson's Disease.* Michael J. Fox Foundation
- Kish, S.J., Mundo, E. & Houle, S.** *Does Ecstasy Damage Brain Serotonin Neurons in Young, Chronic Users of the Drug? A Pilot Study.* Canadian Psychiatric Research Foundation
- Kish, S.J., Mundo, E., Warsh, J., Saint-Cyr, J., Houle, S., Blake, J., Schapiro, C. & Wilson, A.** *Do Serotonin Transporter Gene Polymorphisms Influence Transporter Expression in Human Brain? Canadian Institutes of Health Research*
- Korman, L., Collins, J., McMains, S., Skinner, W. & Toneatto, T.** *Concurrent Gambling, Substance Use and Anger: Development of a Brief Integrated Treatment.* Ontario Problem Gambling Research Centre
- Kovaks, M., Vetro, A., Kennedy, J.L., Barr, C.L. & Devlin, B.** *Risk Factors in Childhood Onset Depression.* National Institutes of Health (Subgrant Agreement with University of Pittsburgh)
- Krank, M., Lai, D., Stacy, A., Wall, A.M. & Wekerle, C.** *A Longitudinal Study of Social Context, Cognition, Risk-Taking Behaviour, and Health Outcomes.* Social Sciences and Humanities Research Council of Canada/ National Health Research and Development Program
- Lalumière, M.L. & Coté, K.** *The Influence of Birth Order on Development: A Study of Adoptees.* Social Sciences and Humanities Research Council of Canada
- Langmuir, J.** *The Effect of a Music Intervention on Agitated and Aggressive Behaviour at Mealtime with Clients Having Severe Neuropsychiatric Disorders.* Canadian Music Therapy Trust Fund
- Lau, M., Christensen, B., Gemar, M. & Segal, Z.** *Inhibitory Deficits in Persons with Major Depressive Disorder: Risk Factor or Correlate? Canadian Institutes of Health Research*
- Le, A.D.** *Role of Serotonin in Stress-Induced Relapse to Alcohol.* Ontario Mental Health Foundation
- Levitan, R.D.** *Serotonin Genetic Variation and Increased Eating Behaviour in Bulimia Nervosa and Seasonal Affective Disorder.* Ontario Mental Health Foundation
- Levitan, R.D.** *Serotonin-Induced Ca²⁺ Mobilization in Platelets: A Biochemical Phenotype to Study Bulimia Nervosa and Seasonal Affective Disorder.* National Alliance for Research on Schizophrenia and Depression
- Levitan, R.D. & Lam, R.** *A Multi-Centre Randomized Control Trial of Light Therapy vs. Anti-Depressants for SAD (sub-grant with University of British Columbia).* University of British Columbia
- Levitan, R.D., Masellis, M., Kennedy, S.H., Kaplan, A.S., Lam, R., Basile, V. & Macciardi, F.** *Polymorphism in Serotonin System Genes: Putative Role in Increased Food Intake in Bulimia Nervosa (BN) and Seasonal Affective Disorder.* Ontario Mental Health Foundation
- Lin, E. & Boyer, R.** *Canadian Community Health Survey — Sensitivity Training and On-Going Support.* Statistics Canada
- Liu, F.** *Ligand-Gated GABA-A and Dopamine D5 Receptor Protein-Protein Interaction in Post-Mortem Schizophrenia Brain.* National Alliance for Research on Schizophrenia and Depression
- Liu, F.** *Novel Model of G-Protein Coupled Receptor and Ligand Gated Ion Channel Cross-Talk.* Canadian Institutes of Health Research
- Liu, S.C.I.** *Altered Gene Expression in Schizophrenia.* Canadian Institutes of Health Research
- Macciardi, F.M.** *Haplotype Transmission Disequilibrium Test (H-TDT) of Candidate Genes for the Susceptibility to Schizophrenia on Chromosome 22q11.* National Alliance for Research on Schizophrenia and Depression
- Macciardi, F.M., Bradwejn, J., Kennedy, J.L. & Koszycki, D.** *Genetic Factors in Panic Disorders.* Canadian Institutes of Health Research
- Macdonald, J. & Turner, N.** *Life Skills, Mathematical Reasoning and Critical Thinking.* Ontario Problem Gambling Research Centre
- MacDonald, J. & Van Tol, H.H.M.** *Calcium-Sensing in Hippocampal Neurons.* Canadian Institutes of Health Research

- MacDonald, J.F., Atwood, H.L., Boulianne, G.L., Charlton, M.P., Roder, J., Trimble, W.S., Van Tol, H.H.M., Wang, Y.T. & Wang, L.T.** *The Synapse*. Canadian Institutes of Health Research
- MacDonald, S.A.** *Impact of Drug and Alcohol Abuse on Traffic Collisions and the Effects of Treatment*. Canadian Institutes of Health Research
- Malla, A., Norman, R., Zipursky, R., Archie, S., Roy, P. & Sylvestre, J.** *Tracking Service Use and Outcomes from First Episode Psychosis in Ontario*. Ontario Mental Health Foundation
- Mann, R.E.** *Evaluation of the Back On Track Assessment Process*. Ontario Remedial Measures Program
- Martucci, L.** *Pharmacogenetics of Antipsychotic Medication Response in Schizophrenia*. Canadian Institutes of Health Research
- Mayberg, H.S., Kennedy, S.H. & Segal, Z.V.** *Limbic-Cortical Metabolic Changes as a Final Common Pathway of Depression Remission: A Comparison of Venlafaxine and Cognitive Behavioural Therapy*. Canadian Institutes of Health Research
- Meyer, J.** *5-HT₂ Receptors in Depression Before and After Treatment*. Canadian Institutes of Health Research
- Meyer, J.** *5-HT_{2A} Receptors in Suicidality and Impulsivity (Fellowship)*. Canadian Institutes of Health Research
- Meyer, J., Houle, S. & Kennedy, S.H.** *5-HT_{2A} Receptors in Suicidality and Impulsivity*. Canadian Institutes of Health Research
- Meyer, J., Houle, S., Wilson, A. & Ginovart, N.** *Occupancy of the Serotonin Transporter by Fluoxetine and Citalopram*. Eli Lilly Canada Inc.
- Meyer, J., Kennedy, S.H., Mayberg, H. & Houle, S.** *5-HT_{2A} Receptors and Treatment Responsiveness during Depression*. National Alliance for Research on Schizophrenia and Depression
- Miller, B., DeWit, D., Macdonald, S., Maguin, G. & Safyer, A.** *Family-Based Prevention for Children of Alcoholics*. National Institute on Alcohol Abuse and Alcoholism
- Millson, M., Myers, T., Calzavara, L., Strike, C. & Cavellieri, W.** *Understanding Injection Drug Using in Toronto: Injection Drug Users' Descriptions of Their Experiences and Perceptions of HIV Risk and Prevention*. Ontario HIV Treatment Network
- Millson, M., Strike, C., Fischer, B., Myers, T. & Calzavara, L.** *Assessing the Impact of Low Threshold Methadone Programs on HIV Risk Taking Behaviours*. National Health Research and Development Program (CIHR)
- Myers, T., Bullock, S., Calzavara, L., Fischer, B. & Millson, P.** *Dual Risk for HIV? Drug Use and Sexual Behaviour among MSM in Toronto*. Ontario HIV Treatment Network
- Naranjo, C., Busto, U., Mayberg, H. & Herrmann, N.** *Brain Reward System Dysfunction in Major Depressive Disorder: An f-MRI Study*. Canadian Institutes of Health Research
- Ni, X.** *Searching for Major Susceptibility Genes for Bipolar Disorder Differential Screening of Gene Initiation Sequences*. Canadian Psychiatric Research Foundation
- Nobrega, J.** *Brain Substrates of Side Effect Vulnerability after Long-Term Neuroleptic Treatment*. National Alliance for Research on Schizophrenia and Depression
- Nobrega, J.** *Brain Thyroid Hormones in Models of Depression*. Ontario Mental Health Foundation
- Noh, S., Kaspar, V. & Morton, B.** *Immigration Resettlement and Mental Health: Assessing Resettlement Impact*. Canadian Institutes of Health Research
- O'Gorman, K. & Buskard, P.** *Overcoming Barriers: Rural Women, HIV and Substance Use*. Ontario HIV Treatment Network
- O'Loughlin, J. & Tyndale, R.F.** *A Prospective Study on the Natural History of Tobacco Dependence*. Canadian Institutes of Health Research
- O'Loughlin, J., Paradis, G., Hanley, J., DiFranza, J., Tyndale, R.F., Clarke, P., Sacks-Silver, G., Tremblay, M., Heneman, B., Dupuis, G., Bujold, M., Band, P. & Dery, V.** *A Prospective Study on the Natural History of Nicotine Dependence*. National Cancer Institute of Canada
- Palmour, R.M., Vaccarino, F.J., Bateson, A.N., Baker, G.B., Ervin, F., Gutkowska, J. & Chaudhuri, A.** *cck and Anxiety: Neurobiological Characterization*. Canadian Institutes of Health Research
- Parikh, S.** *Developing a Treatment Optimization Program: Integration of Patient and Provider Interventions*. Ontario Mental Health Foundation
- Parikh, S. & Zaretsky, A.** *Cognitive-Behavioural Therapy versus Psychoeducation in Bipolar Disorder*. Stanley Research Foundation
- Paterson, A. & Pei, Y.** *Genetic Mapping of Type 1 Diabetes Susceptibility Loci on Human Chromosomes 3 and 4*. Canadian Diabetes Association
- Perkins, D.O., Zipursky, R.B., Charles, C. & Lieberman, J.** *Prospective MRI and MRS Neuroimaging in Patients Prodromal to Schizophrenia*. Stanley Research Foundation
- Petronis, A.** *Epigenetic Analysis of Class III VNTR Alleles of the Insulin Gene*. Juvenile Diabetes Foundation International
- Petronis, A.** *Epigenetic Regulation of the Tumor Necrosis Factor Gene in Crohn's Disease*. Crohn's and Colitis Foundation of Canada
- Petronis, A.** *Epigenetic Search for Retroviruses in Major Psychosis*. Stanley Research Foundation
- Petronis, A.** *Epigenetic Studies of the Serotonin Receptor 2A Gene in Schizophrenia*. National Alliance for Research on Schizophrenia and Depression
- Petronis, A.** *Search for Genetic and Epigenetic Risk Factors in Major Psychosis*. Ontario Mental Health Foundation

- Rahman, S. & Corrigan, W.A.** *Dopamine and Non-Dopamine Mechanisms of Nicotine Addiction: Microdialysis Study*. University of Toronto (Research Services)
- Rector, N.A., Denisoff, E., Casley-Rondi, G., Dorian, B. & Bagby, R.M.** *Cognitive Processes and Therapy in Post-Traumatic Stress Disorder*. Workplace Safety and Insurance Board
- Rector, N.A., Richter, M., Gemar, M. & Denisoff, E.** *Cognitive and Behavioural Treatment of Obsessive-Compulsive Disorder: The Role of Cognitive Factors in Treatment Response and Relapse Prevention*. Canadian Institutes of Health Research
- Remington, G. & Kapur, S.** *Augmentation of Clozapine Partial Responders with Tetrabenazine*. Stanley Research Foundation
- Remington, G. & Kapur, S.** *Janssen-Ortho Clinical Research Fellowship*. Janssen-Ortho Inc.
- Richter, M.A.** *Obsessive-Compulsive Disorder: An Innovative Genetic Study*. Ontario Mental Health Foundation
- Richter, M.A., Kennedy, J. & Swinson, R.P.** *Identifying the Genetic Basis of Obsessive-Compulsive Disorder*. Canadian Institutes of Health Research
- Roder, J., Carlen, P., Hampson, D., Marks, A., McDonald, R., Pawson, T., Ralph, M., Salter, M., Smith, C., St. George-Hyslop, P., Van Tol, H.H.M. & Wojtowicz, M.** *Place Cell Equipment*. Canadian Institutes of Health Research
- Rootman, I., Ferrence, R., Ashley, M.J., Brown, K.S., Cohen, J., McDonald, P. & Stephens, T.** *Ontario Tobacco Research Unit*. Ontario Ministry of Health and Long-Term Care
- Rootman, I., Ferrence, R., Ashley, M.J., Brown, K.S., Cohen, J., McDonald, P. & Stephens, T.** *Plans for Enhanced Surveillance, Evaluation and Research*. Ontario Ministry of Health and Long-Term Care
- Ross, B.** *Abnormal Phospholipid Dependent Signaling in Schizophrenia: Potential for Novel Therapeutic Approaches (New Investigator Fellowship)*. Ontario Mental Health Foundation
- Ross, B.** *Schizophrenia, Eicosanoids and Nicotine Acid*. Ontario Mental Health Foundation
- Rotzinger, S.** *The Role of Glutamate and CRF Projections in the Amygdala in Anxiety*. Alberta Heritage Foundation for Medical Research
- Rummens, J.** *The Canadian Identities Database (CID)*. Public Works and Government Services
- Rummens, J.** *Who ARE I? Identity Formation and Negotiation among New Canadian Youth*. Canadian Heritage (Multiculturalism)
- Rummens, J. & Seat, R.** *Assessing the Impact of the Kosovo Crisis on the Mental Health and Well Being of Newcomer Serbian Children in the Greater Toronto Area*. The Joint Centre of Excellence for Research on Immigration and Settlement (CERIS)
- Rummens, J., Rajko, S., Beiser, M., Noh, S. & Kaspar, V.** *Equal but Not Equal, Neighbours and Yet Not Friends: Assessing the Impact of the Kosovo Crisis on the Mental Health and Well-Being of Newcomer Serbian Children in the Toronto Area*. Social Sciences and Humanities Research Council of Canada
- Rush, B.** *Monitoring the Substance Abuse Treatment System in Ontario Using the Drug and Alcohol Treatment Information System*. Ontario Ministry of Health and Long-Term Care — Ontario Substance Abuse Bureau
- Rush, B., Norman, R., Kirsch, B. & Wild, C.** *Assessing the Critical Characteristics of Community Support Programs for People with Severe Mental Illness*. Ontario Mental Health Foundation
- Schechter, M., Anis, A., Brisette, S., Brochu, S., Fischer, B., Hankins, C., Lauzon, P., Marsh, D., O'Shaughnessy, M. & Rehm, J.** *Multi-centre, Randomized Controlled Trial of Heroin Assisted Therapy for Treatment-Refractory Injection Opiate Users*. Canadian Institutes of Health Research
- Segal, Z.** *Predicting Depressive Relapse through Cognitive Changes following Mood Induction*. Ontario Mental Health Foundation
- Segal, Z., Gemar, M. & Kennedy, S.H.** *Predicting Depressive Relapse through Cognitive Changes following Mood Challenge*. Canadian Institutes of Health Research
- Selby, P.** *Tobacco Control Programme/Prevention, Cessation and Education*. Health Canada
- Seto, M.C., Barbaree, H.E., Schneider, R., Lalumière, M.L., Rice, M.E., Harris, G.T. & Hilton, N.Z.** *Demands on Forensic Mental Health Services in Ontario*. Ontario Mental Health Foundation
- Shain, M. & Suurvali, H.** *Investing in Comprehensive Workplace Health Promotion: A Resource*. Health Canada
- Shain, M. & Weil, S.** *Evaluating an Alternative to Long Term Suspension Program*. Ontario Trillium Foundation
- Simich, L. & Beiser, M.** *A Study of Secondary Migration in Ontario*. Settlement and Integration Services, Citizenship and Immigration Canada
- Skinner, W. & Ferentzy, P.** *Exploring Mutual Aid Pathways to Recovery from Gambling Problems and Co-occurring Gambling and Substance Abuse Problems*. Ontario Problem Gambling Research Centre
- Smart, R.G., Mann, R.E., Beirness, D., Chipman, M., Dussault, C., Tasca, L., Mercer, W., Solomon, R. & Vingilis, E.** *Anti-Social Behaviour and the Automobile*. Networks of Centres of Excellence Program
- Stewart, M. & Beiser, M.** *Multicultural Meaning of Social Support among Immigrants and Refugees*. Social Sciences and Humanities Research Council of Canada

- Stewart, S.H., Klein, R.M. & Zack, M.** *Contribution of Attentional Mechanisms to Understanding Relations between Disordered Gambling Behaviour and Alcohol Misuse.* Ontario Problem Gambling Research Centre
- Strauss, J. & Kennedy, J.L.** *Brain Derived Neurotrophic Factor: A Candidate for Childhood-Onset Depression.* Canadian Institutes of Health Research
- Strike, C.** *Access to Health and Mental Health Services: The Perspective of Suicidal Men.* Distress Centres of Ontario
- Sylvestre, J., Trainor, J., Ilves, P., Aubry, T., George, L. & Nelson, G.** *An Evaluation of Housing Programs in Ontario.* Ontario Mental Health Foundation
- Tolomiczenko, G.** *Young Investigator Award.* National Alliance for Research on Schizophrenia and Depression
- Tolomiczenko, G. & Dewa, C.** *Mental Health Court Diversion Evaluation Project.* Ontario Mental Health Foundation
- Tomkins, D. & O'Neil, M.** *Ethanol Reinforcement: The Role of 5-HT_{1B} Receptors.* National Institute on Alcohol Abuse and Alcoholism
- Tomkins, D., Nobrega, J. & Tyndale, R.** *Influence of Genetic and Neuroadaptations in Alcohol Drinking: A Role for GABA_A Receptors.* Ontario Mental Health Foundation
- Toneatto, T.** *A Controlled Evaluation of Cognitive Therapy for Problem Gambling.* Ontario Problem Gambling Research Centre
- Toneatto, T., Brands, B., Selby, P. & Sinclair, D.** *A Randomized, Double-Blind, Placebo-Controlled Trial of Naltrexone in the Treatment of Concurrent Alcohol Dependence and Pathological Gambling.* Ontario Problem Gambling Research Centre
- Trainor, J., Sylvestre, J. & Ilves, P.** *Housing Stability and Mental Illness.* Canada Mortgage and Housing Corporation
- Turner, N., Littman-Sharp, N. & Zangeneh, M.** *Winners: Why Do Some Develop Problems While Others Do Not.* Ontario Ministry of Health and Long-Term Care
- Turrone, P., Remington, G., Nobrega, J. & Kapur, S.** *Revisiting the vcm Model of Tardive Dyskinesia: Relationship to D₂ Receptor Occupancy.* AstraZeneca Canada Inc.
- Tyndale, R.** *Canada Research Chair (Tier II).* Canadian Institutes of Health Research
- Tyndale, R.F.** *Drug Metabolism in the Brain: Expression and Regulation of Cytochromes P450.* Canadian Institutes of Health Research
- Tyndale, R.F. & Sellers, E.M.** *Pharmacogenetic Risk Factors in Drug Abuse; CYP Variants Supplement.* National Institute on Drug Abuse
- Tyndale, R.F. & Sellers, E.M.** *Pharmacogenetics Risk Factors in Drug Abuse; CYP Variants.* National Institute on Drug Abuse
- Tyndale, R.F. & Sellers, E.M.** *Pharmacogenetics: CYP2A6 Genetic Variants Alter Smoking.* Canadian Institutes of Health Research
- Vaccarino, F.** *Ontario Research Performance Funds.* Ontario Ministry of Energy, Science and Technology and University of Toronto
- Vaccarino, F.J.** *GRF: Behavioural and Physiological Characterization.* Natural Sciences and Engineering Research Council
- Vaccarino, F.J.** *The Role of cck in Psychostimulant Drug Craving.* Canadian Institutes of Health Research
- Vaccarino, F.J. & Rotzinger, S.** *Neurobiology of the Opposing Motivational Effects of Stress on Psychostimulant Self-Administration.* Canadian Institutes of Health Research
- Vaccarino, F.J., Arifuzzaman, A., Vichnevetski, K. & Rayfield, C.** *Intellectual Property Management Program.* Canadian Institutes of Health Research
- Vaccarino, F.J., Palmour, R.M. & Ervin, F.** *cck and Anxiety: Neurobehavioural Characterization.* Canadian Institutes of Health Research
- Van Tol, H.H.M.** *Canada Research Chair (Tier I).* Canadian Institutes of Health Research – Canada Research Chairs Program
- Van Tol, H.H.M.** *SH3 Domain Interactions in Dopamine Receptors.* Canadian Institutes of Health Research
- Van Tol, H.H.M.** *The Kir3 – Dopamine Receptor Complex.* Canadian Institutes of Health Research
- Van Tol, H.H.M., Niznik, H.B. & Kennedy, J.L.** *Dopamine and Psychomotor Disease.* Canadian Institutes of Health Research
- Van Tol, H.H.M., Wong, A.H.C. & Macciardi, F.** *Genetic Studies with Candidate Genes in Schizophrenia.* Ontario Mental Health Foundation
- Verhoeff, N.P.** *Imaging Seriatial Synaptic Dopamine Levels and Dopamine D₂ Receptor Binding Potential in Schizophrenia Patients and in Control Subjects Using (“C) Raclopride PET (Postdoctoral Research Fellowship).* Ontario Mental Health Foundation
- Verhoeff, N.P.** *Young Investigator Award.* National Alliance for Research on Schizophrenia and Depression
- Vincent, J. & Petronis, A.** *Investigating the Role of the sca8 Locus in Major Psychosis.* Ontario Mental Health Foundation
- Vingilis, E., Mann, R., McLeod, A., Seeley, J., Beirness, D., Girling, S., Gliksman, L., Lane, P., Lamble, R., Single, E., Stoduto, G. & Voas, R.** *Health/Safety Impact of Ontario's Drinking Hours.* National Institutes of Health — National Institute on Alcohol Abuse and Alcoholism
- Warner, J. & Adlaf, E.** *Narratives of Gender and Aggression in a Maritime Town.* Social Sciences and Humanities Research Council of Canada

- Warsh, J.** *Calcium Homeostasis and G-Protein-Coupled cAMP Signaling Disturbances in Bipolar Affective Disorder*. Canadian Institutes of Health Research
- Warsh, J.** *Diagnostic Specificity of B Lymphoblast Calcium Abnormalities to Bipolar Disorder*. Ontario Mental Health Foundation
- Warsh, J. & Li, P.** *Effect of Antipolar Medications on Cellular and Molecular Mechanisms Modulating Intracellular Calcium Signalling*. Canadian Institutes of Health Research
- Wekerle, C.** *Common Risk Factors in Alcohol Use, Abuse, and Intimate Violence*. Ontario Mental Health Foundation
- Wekerle, C. & Goldstein, A.** *Outcome Evaluation of the Tools of Awareness Program*. Speers Society
- Wekerle, C., Wall, A.M., MacMillan, H. & Trocme, N.** *Maltreatment and Adolescent Pathways (MAP) Project*. Canadian Institutes of Health Research
- Wherret, D., Zucker, K.J., Bradley, S.J. & Nielson, B.** *Psychosocial Adjustment and Gender Identity in Genetic Males Born with Ambiguous Genitalia*. The Hospital for Sick Children Research Institute
- Whitehead, P.C., White, J., Maxim, P. & Ferrence, R.** *Exploring Social Cohesion in a Globalizing Era*. Social Sciences and Humanities Research Council of Canada
- Wilson, A. & Ginovart, N.** *Norepinephrine Transporter Radioligand — Part I: Development of Effective Radiotracers for Imaging the Norepinephrine Transporter (NET) Using Positron Emission Tomography (PET)*. Eli Lilly Canada Inc.
- Wong, A.** *Genetic Studies with Candidate Genes in Schizophrenia*. Ontario Mental Health Foundation
- Wong, A. & Van Tol, H.** *Candidate Genes and Linkage Disequilibrium Studies in Schizophrenia (Clinician Scientist Award)*. Canadian Institutes of Health Research
- Wu, Z., Kaspar, V., Noh, S. & Chen, J.** *Immigrants, Selectivity and Mental Health*. Canadian Population Health Initiative
- Yu, X.M.** *CIHR Scholarship*. Canadian Institutes of Health Research
- Yu, X.M.** *Direct Binding of Dopamine D₅ to GABA_A Receptor and Its Function*. Canadian Institutes of Health Research
- Yu, X.M.** *Functional Sodium-Calcium Interaction in the Regulation of NMDA Channel Activity*. Ontario Neurotrauma Foundation
- Yu, X.M.** *Regulation of NMDA Receptors by Intracellular Sodium*. Canadian Institutes of Health Research
- Zack, M., Stewart, S.H. & Klein, R.** *Contributions of Attentional Mechanisms to Understanding Relations between Disordered Gambling Behaviour and Alcohol Misuse (sub-grant with Dalhousie University)*. Ontario Problem Gambling Research Centre
- Zangeneh, M. & Sadeghi, N.** *Exploration of Cultural Perceptions, Attitudes and Beliefs Regarding Gambling and Problem Gambling in the Iranian Community (Exploratory Study)*. Ontario Problem Gambling Research Centre
- Zipursky, R.B., Epstein, I., Kumra, S., Lewis, R. & Christensen, B.** *Delaying or Preventing Psychosis Onset: A Randomized Double-Blind Comparison of Olanzapine and Placebo in Persons Prodromal to Psychosis*. Eli Lilly Canada Inc.
- Zipursky, R.B., Lieberman, J., Green, A., Sharma, T. & Christensen, B.** *Assessments of Normal Controls for Comparison in Assessments of Acute and Long-Term Efficacy of Olanzapine in First-Episode Psychotic Disorders: A Randomized Double-Blind Comparison with Haloperidol*. Eli Lilly Canada Inc.

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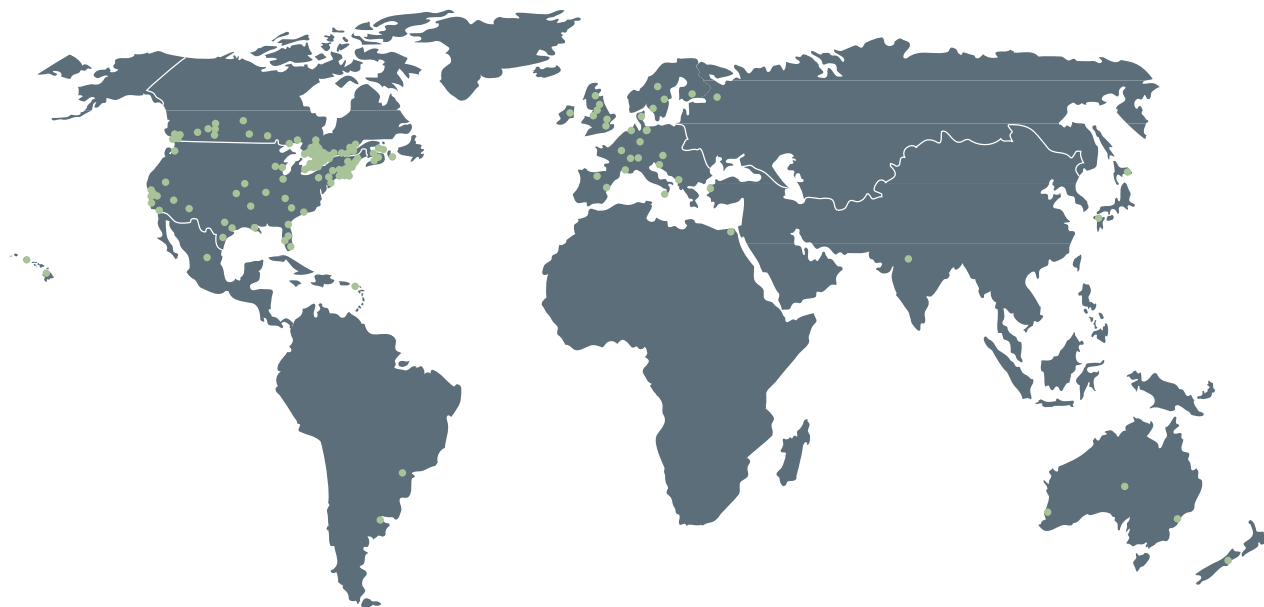
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