Innovations in the Science of Cannabis Conference

FEBRUARY 9-10, 2018

St. Joseph’s Healthcare Hamilton | West 5th Campus | 100 West 5th Street | Hamilton, Ontario, Canada

Jason Busse, DC, PhD
Co-Director

James MacKillop, PhD
Co-Director
Acknowledgments

- Michael G. DeGroote
- Dr. John Kelton and Sarrah Lal
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- Dr. Paul O’Byrne
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- Invited speakers
Disclosures

- **Jason Busse, DC, PhD**
  - Research funding from CIHR and MGD IRPC
  - No consultancies or ownership to commercial cannabis entities

- **James MacKillop, PhD**
  - Research funding from CIHR, NIH, RGCO, GREO, CSC
  - No consultancies or ownership to commercial cannabis entities

- No conference-level conflicts of interest to disclose.
  - Funded by registration revenue and philanthropy
Overview

- Brief history and context

- Priorities for the Michael G. DeGroote Centre for Medicinal Cannabis Research

- Innovations in the Science of Cannabis
Brief Canadian Legislative History

- Geneva International Convention on Narcotics Control (1925)
- Medical Marihuana Access Regulations (MMAR) (2001)
- Marihuana for Medical Purposes Regulations (MMPR) (2014)
- Federal Legalization (2018)
Brief Canadian Legislative History

1925

Geneva International Convention on Narcotics Control

2001

Marihuana for Medical Purposes Regulations (MMPR)

2014

Medical Marihuana Access Regulations (MMAR)

2017

Access to Cannabis for Medical Purposes Regulations (ACMPR)

2018

Federal Legalization

Registered Medical Cannabis Users, 2014-2017 (Health Canada)
Registered Medical Cannabis Users, 2014-2017 (Health Canada)
Smoked cannabis for chronic neuropathic pain: a randomized controlled trial

Mark A. Ware MBBS, Tongtong Wang PhD, Stan Shapiro PhD, Ann Robinson RN, Thierry Ducruet MSc, Thao Huynh MD, Ann Gamsa PhD, Gary J. Bennett PhD, Jean-Paul Collet MD PhD

Table 2: Pairwise comparisons of the effects of four potencies of smoked cannabis on average daily pain

<table>
<thead>
<tr>
<th>Potency, % of THC</th>
<th>0</th>
<th>2.5</th>
<th>6.0</th>
<th>9.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2.5</td>
<td>-0.13 (-0.83 to 0.56)</td>
<td>-</td>
<td>-0.04 (-0.64 to 0.73)</td>
<td>-</td>
</tr>
<tr>
<td>6.0</td>
<td>-0.09 (-0.78 to 0.60)</td>
<td>0.04 (-1.27 to 0.11)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>9.4</td>
<td>-0.71 (-1.40 to -0.02)</td>
<td>-0.58 (-1.30 to 0.06)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Note: CI = confidence interval, THC = tetrahydrocannabinol.
Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome

Orrin Devinsky, M.D., J. Helen Cross, Ph.D., F.R.C.P.C.H., Linda Laux, M.D., Eric Marsh, M.D., Ian Miller, M.D., Rima Nabbout, M.D., Ingrid E. Scheffer, M.B., B.S., Ph.D., Elizabeth A. Thiele, M.D., Ph.D., and Stephen Wright, M.D., for the Cannabidiol in Dravet Syndrome Study Group

Table 2. Primary Efficacy End Point of Percentage Change in Convulsive-Seizure Frequency in Each Trial Group.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cannabidiol</th>
<th>Placebo</th>
<th>Adjusted Median Difference (95% CI)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of convulsive seizures per mo</td>
<td>12.4 (3.9 to 1717)</td>
<td>14.9 (3.7 to 718)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>— median (range)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>12.4 (3.9 to 1717)</td>
<td>14.9 (3.7 to 718)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment period</td>
<td>5.9 (0.0 to 2159)</td>
<td>14.1 (0.9 to 709)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage change in seizure fre-</td>
<td>−38.9 (−100 to 337)</td>
<td>−13.3 (−91.5 to 230)</td>
<td>−22.8 (−41.1 to −5.4)</td>
<td>0.01</td>
</tr>
<tr>
<td>quency — median (range)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Low Quality Evidence of Overall Efficacy

Of 79 trials, 4 judged to have low risk of bias

Increased risk of short-term AEs

Low quality evidence in general

Moderate quality evidence for pain and spasticity

Cannabinoids for Medical Use
A Systematic Review and Meta-analysis

Penny F. Whiting, PhD; Robert F. Wolff, MD; Sohan Deshpande, MSc; Marcello Di Nisio, PhD; Steven Duffy, PgD; Adrian V. Hernandez, MD, PhD; J. Christiaan Keurentjes, MD, PhD; Shona Lang, PhD; Kate Misso, MSc; Steve Ryder, MSc; Simone Schmidtkofer, MSc; Marie Westwood, PhD; Jos Kleijnen, MD, PhD

IMPORTANCE Cannabis and cannabinoid drugs are widely used to treat disease or alleviate symptoms, but their efficacy for specific indications is not clear.

OBJECTIVE To conduct a systematic review of the benefits and adverse events (AEs) of cannabinoids.

DATA SOURCES Twenty-eight databases from inception to April 2015.
# Known Adverse Effects

Table 2. Level of Confidence in the Evidence for Adverse Effects of Marijuana on Health and Well-Being.

<table>
<thead>
<tr>
<th>Effect</th>
<th>Overall Level of Confidence*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addiction to marijuana and other substances</td>
<td>High</td>
</tr>
<tr>
<td>Abnormal brain development</td>
<td>Medium</td>
</tr>
<tr>
<td>Progression to use of other drugs</td>
<td>Medium</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>Medium</td>
</tr>
<tr>
<td>Depression or anxiety</td>
<td>Medium</td>
</tr>
<tr>
<td>Diminished lifetime achievement</td>
<td>High</td>
</tr>
<tr>
<td>Motor vehicle accidents</td>
<td>High</td>
</tr>
<tr>
<td>Symptoms of chronic bronchitis</td>
<td>High</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>Low</td>
</tr>
</tbody>
</table>

Prevalence of Cannabis Use Disorder in Canada

<table>
<thead>
<tr>
<th></th>
<th>Lifetime</th>
<th>12-Month</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6.8%</td>
<td>1.3%</td>
</tr>
</tbody>
</table>

Statistics Canada, 82-624-X and 82-003-X; Volkow et al., 2014 NEJM
Opioid Consumption by Country

*Standard daily opioid dose for every 1 million people*

- United States
- Canada
- Germany
- Denmark
- Belgium
- Austria
- Switzerland
- Australia
- Holland
- Spain
- Luxembourg
- Norway
- Great Britain
- Ireland
- New Zealand
- Sweden
- Iceland
- Israel
- France
- Slovenia
- Portugal
- Finland
- Italy
- Mauritius
- Greece

Source: United Nations International Narcotics Control Board; Figure: Sarah Frostenson, Vox
Opioid Overdose Deaths in Ontario, 2002-2014

Figure: Leece & Kahan, 2016

<table>
<thead>
<tr>
<th>Codeine</th>
<th>Fentanyl</th>
<th>Heroin</th>
<th>Hydromorphone</th>
<th>Methadone</th>
<th>Morphine</th>
<th>Oxycodone</th>
</tr>
</thead>
<tbody>
<tr>
<td>+233%</td>
<td>+1660%</td>
<td>+334%</td>
<td>+600%</td>
<td>+84%</td>
<td>+124%</td>
<td>+370%</td>
</tr>
</tbody>
</table>
Opioid Overdose Deaths in the United States

Source: Centers for Disease Control and Prevention
Opioid Overdose Deaths in the United States

Total U.S. drug deaths

60,000 deaths per year

40,000

20,000


Around 64,000 people died from drug overdoses in the U.S. in 2016.

Peak car crash deaths (1972)

Peak H.I.V. deaths (1995)

Peak gun deaths (1993)
Guideline for opioid therapy and chronic noncancer pain

GUIDELINE CPD

Jason W. Busse DC PhD, Samantha Craigie MSc, David N. Juurlink MD PhD, D. Norman Buckley MD, Li Wang PhD, Rachel J. Couban MA MSt, Thomas Agoritsas MD PhD, Elie A. Akl MD PhD, Alonso Carrasco-Labra DDS MSc, Lynn Cooper BES, Chris Cull, Bruno R. da Costa PT PhD, Joseph W. Frank MD MPH, Gus Grant AB LLB MD, Alfonso Iorio MD PhD, Navindra Persaud MD MSc, Sol Stern MD, Peter Tugwell MD MSc, Per Olav Vandvik MD PhD, Gordon H. Guyatt MD MSc


CMAJ podcasts: author interview at https://soundcloud.com/cmajpodcasts/170363-guide


Chronic noncancer pain includes any painful condition that persists for at least three months and is not associated with malignant disease. According to seven national surveys conducted between 1994 and 2008, 15%-19% of Canadian

KEY POINTS
- We recommend optimization of nonopioid pharmacotherapy and nonpharmacologic therapy, rather than a trial of opioids.
Widespread Existing Use and Patient Interest

Opioids Out, Cannabis In: Negotiating the Unknowns in Patient Care for Chronic Pain

Esther K. Choo, MD, MPH
Center for Policy and Research in Emergency Medicine, Oregon Health & Science University, Portland.

Sarah W. Feldstein Ewing, PhD
Department of Psychiatry, Oregon Health & Science University, Portland.

Travis L. Lovejoy, PhD, MPH
Department of Psychiatry, Oregon Health & Science University, Portland; and Center to Improve Veteran Involvement in Care, VA Portland Health Care System, Portland, Oregon.

With the current nationwide epidemic of opioid abuse, dependence, and fatalities, clinicians are being asked by federal agencies and professional societies to control their prescribing of narcotic medications for pain. Federal guidelines emphasize tapering, discontinuing, and limiting initiation of these drugs except in provision of end-of-life care. Reducing reliance on opioids, however, is a massive task. According to one estimate, more than 650,000 opioid prescriptions are dispensed each day in the United States. Unless the nation develops an increased tolerance to chronic pain, reduction in opioid prescribing leaves a vacuum that will be filled with other therapies.

Enter cannabis. As of August 2016, the District of Columbia and 25 states have legalized cannabis for medical use. Recreational use of cannabis has been legalized in 4 of these states and Washington, DC, and may lack awareness about the potential harms of cannabis, parameters for safe use, interactions with other medications, and initiation or escalation of THC (Δ9-tetrahydrocannabinol) dosing and thus report poor self-efficacy in prescribing and guiding cannabis use for pain and other therapeutic purposes. Although current evidence supports cannabis use for a limited number of conditions, (eg, chronic pain, muscle spasticity), medical cannabis has been approved by individual states for a wide variety of indications, including anorexia in HIV/AIDS, depression and anxiety disorders, psychosis, insomnia, glaucoma, Parkinson disease, seizures, Tourette syndrome, rheumatoid arthritis, traumatic brain injury, myasthenia gravis, and a host of autoimmune and neuromuscular conditions.

Therefore, physicians may be placed in the uncomfortable position of explaining to patients why they might advise against treatment that appears to be endorsed by a governing body (eg, health department of states in which medicinal use has been legalized) rather than supported by science. The ongoing federal ban on cannabis that recently was reinforced by the US Drug Enforcement Agency creates added complexity for physicians. Inconsistency across individual practitioners and health agencies regarding how to approach this substance

Viewpoint page 1765

Choo et al. 2016, JAMA
Complexities of Cannabis

PHARMACODYNAMICS

Compound(s)

PHARMACOKINETICS

Formulation/RoA

Acute and Chronic Effects (Positive and Negative)
Complexities of Cannabis

**PHARMACODYNAMICS**

Cocaine

**PHARMACOKINETICS**

Inhalation

Intranasal

Intravenous

Acute and Chronic Effects (Positive and Negative)
Complexities of Cannabis

**PHARMACODYNAMICS**

Nicotine

**PHARMACOKINETICS**

Inhalation
Oral
Intranasal
Transdermal

**Acute and Chronic Effects (Positive and Negative)**
Complexities of Cannabis

**PHARMACODYNAMICS**

- Cannabis
  - >500 active compounds (!)

**PHARMACOKINETICS**

- Inhalation
- Oral
- Transdermal

- Cigarette
- Pipe
- Waterpipe
- Vaporizer
- Edible
- Oil
- Patch
- Salve

Acute and Chronic Effects (Positive and Negative)
Complexities of Cannabis

**PHARMACODYNAMICS**

- Cannabis

**PHARMACOKINETICS**

- Inhalation
- Oral
- Transdermal

>500 active compounds (!)

CBD

**Acute and Chronic Effects**

(Positive and Negative)

- Cigarette
- Pipe
- Waterpipe
- Vaporizer
- Edible
- Oil
- Patch
- Salve
Complexities of Cannabis

**PHARMACODYNAMICS**

Cannabis

>500 active compounds (!)

CBC

**PHARMACOKINETICS**

Inhalation

Oral

Transdermal

Cigarette

Pipe

Waterpipe

Vaporizer

Edible

Oil

Patch

Salve

Acute and Chronic Effects (Positive and Negative)
Complexities of Cannabis

**PHARMACODYNAMICS**

Cannabis

>500 active compounds (!)

**CBG**

**PHARMACOKINETICS**

Inhalation
Oral
Transdermal

Cigarette
Pipe
Waterpipe
Vaporizer
Edible
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Patch
Salve

Acute and Chronic Effects (Positive and Negative)
Complexities of Cannabis

**PHARMACODYNAMICS**

Cannabis

>500 active compounds (!)

**CBN**

**PHARMACOKINETICS**

- Inhalation
- Oral
- Transdermal

Cigarette
Pipe
Waterpipe
Vaporizer
Edible
Oil
Patch
Salve

Acute and Chronic Effects (Positive and Negative)
Complexities of Cannabis

**Pharmacodynamics**

Cannabis

>500 active compounds (!)

- Myrcene
- Linalool
- α Bisalol
- Borneol
- Caryophyllene
- α Pinene
- β Pinene
- Camphene
- Terpineol
- Δ-3-carene
- Limonene
- Eucalyptol
- Humulene
- Trans-neroliol

**Pharmacokinetics**

Inhalation
Oral
Transdermal

- Cigarette
- Pipe
- Waterpipe
- Vaporizer
- Edible
- Oil
- Patch
- Salve

Acute and Chronic Effects (Positive and Negative)
Escalation in THC Over Time

El-Sohly, 2014; Drug Abuse Warning Network, 2011
New Formulations

“Wax”

“Shatter”

“Budder”

Extractions (40-90% THC)
Vision and Mission

Vision
An evidence-based understanding of medicinal cannabis, encompassing both its potential therapeutic effects and associated risks.

Mission
To leverage the highest standards of research methodology to collectively advance the understanding of medicinal cannabis.

To do this via:
- Curating the collective body of knowledge on medicinal cannabis
- Conducting innovative research projects to advance scientific discovery
- Creating a network of researchers, clinicians, and patients dedicated to evidence-based increasing the clinical understanding of cannabis
Curating the Evidence Base

Research Summaries
Synopses of high impact research publications from clinical and research experts studying cannabis.

Evidence Briefs
Consolidated overviews of the state of medicinal cannabis across various clinical and research areas.

Evidence Syntheses
‘Deep dive' explorations of topics related to medicinal cannabis via the McMaster Health Forum
Conducting Innovative Research

Therapeutic Efficacy

Potential Harms
Priority Areas

**Therapeutic Benefits**
- Knowledge syntheses
- Systematic reviews
- Clinical guidelines
- Preclinical models
- Pilot randomized controlled trials

**Adverse Consequences**
- Cannabis use disorder (addiction)
- Neurocognitive sequelae
- Psychomotor impairment
- Psychosis and other psychiatric disorders

Surveillance Over the Course of Legalization
Priority Areas

**Therapeutic Benefits**

- Knowledge syntheses
- Systematic reviews
- Clinical guidelines
- Preclinical models
- Pilot randomized controlled trials

**Archival Data Reviews**

**Constituent Analysis**

**Translational Screening**

**Cancer Pain**

**Post-surgical Pain**

**Anxiety Disorder**

**Bipolar Disorder**

**Sleep**

**Lupus**
Priority Areas

Genetic Determinants
Novel CUD Treatments

Cognition
Motivation
Development

Alcohol
Criminal Behavior
Gambling
Psychosis

Adverse Consequences

- Cannabis use disorder (addiction)
- Neurocognitive sequelae
- Other psychiatric disorders and adverse consequences
- Psychomotor impairment
Priority Areas

PATH Registry
Population Assessment for Tomorrow’s Health

Middle-aged community adults
*N*=1435, M age = 58% female, 29% cannabis+
Assessment: pre-legalization/+6/+12/+18 mos.

Project Beta

Emerging adult binge drinkers
*N*=453, M age = 21.5, 68% female, 52% cannabis+
Assessment: 11 assessments, every 4 mos.,

datacann
Database for Cannabis Consumption & Study

Authorized cannabis for pain patients
Five clinics in ON, MB, and BC
Assessment: BL, 4/8/12 mos., +6 mos. for 5 years

Surveillance Over the Course of Legalization
Creating a Network
Federal Perspectives and Public Policy

Ms. Rebecca Jesseean  Dr. Wilson Compton  Mr. Michael Devillaer  Dr. Michael Amlung

Preclinical Animal Models

Dr. Andrea Hohmann  Dr. Linda Parker  Dr. Gurmit Singh
Human Brain Imaging

Dr. Sarah Feldstein Ewing

Dr. Bernard LeFoll

Dr. Iris Balodis

Human Psychopharmacology

Dr. Jane Metrik

Dr. Margaret Haney

Dr. Alan Budney
Clinical Applications
Welcome!