

# Medical Cannabis & PTSD;

A TRIPLE-BLIND PHASE 2 CLINICAL TRIAL EXAMINING THE EFFICACY OF CANNABIS OF VARIOUS CHEMICAL COMPOSITION ON THE SYMPTOMS OF PTSD



**Philippe Lucas, MA, PhD Student**

VP of Patient Advocacy, Tilray

Graduate Scholar, Centre for Addictions Research of BC



# Medical Cannabis in Canada

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*R. v. Parker* (2000) - constitutional right to choose cannabis as medicine without fear of criminal sanction.

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In 2001, the *Marihuana Medical Access Regulations* (MMAR).

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To date, approximately 60,000 Canadians have obtained an authorization to possess cannabis for medical purposes.

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1 million Canadians used cannabis for self-defined medical conditions.

(Adlaf, Begin & Sawka, 2005; Belle-Isle & Hathaway, 2007)

# Canadian Medical Marijuana System

**MMAR**  
ENDED  
MARCH 31, 2014



**MMPR**  
STARTED  
APRIL 1, 2014

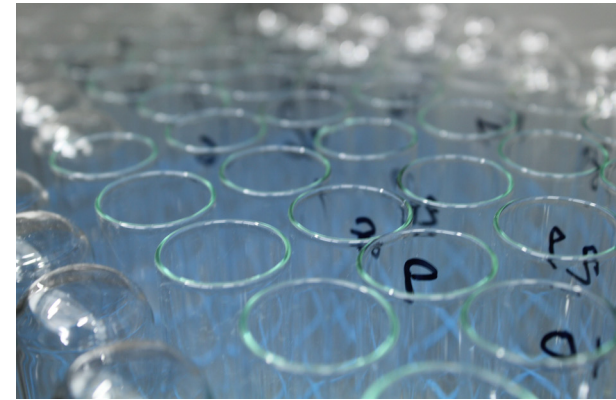


Health Canada Santé Canada

# About Tilray

Tilray is a Health Canada licensed producer of medical cannabis

In April 2014, we began operating a state-of-the-art, \$30 million, 60,000 square foot research and production facility employing more than 140 people from the greater Nanaimo area.



# Tilray Research Program



**Phase 2 placebo-controlled clinical trial agreement** with the University of British Columbia to examine the therapeutic potential of medical cannabis on the symptoms of PTSD.

- 42 participants; military and police veterans and other survivors of physical violence.
- Study will compare vaporized cannabis of varying cannabinoid concentrations to placebo.
- Final ethics approvals in place; recruiting about to begin.

## **Pilot studies of Tilray cannabis-based extracts and preparations**

- Adult Epilepsy, Ontario Brain Institute
- Nausea/vommiting in oncological treatment, New South Wales, Australia

## **Patient patterns of use and cannabis substitution research**

- Tilray Observational Patient Survey (TOPS)
- 20+ sites, >1000 patients

# Dried Cannabis Flower



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There are over 100 unique cannabinoids, the most abundant of which are  $\Delta$ -9-tetrahydrocannabinol (THC) and cannabidiol (CBD).

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Cannabinoids are thought to exert their physiological effects via the endocannabinoid system. THC binds with high affinity to CB1R in the brain, by which it mediates its psychoactive effects.

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Cannabinoid receptors regulate: memory, sleep, anxiety, mood, stress response, inflammation.

# Rationale for Cannabis in the Treatment of PTSD

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Preliminary studies (open-label and observational) suggest a strong potential for the treatment of PTSD with medical cannabis.

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Cannabis was associated with a 75% reduction in 3 areas of PTSD symptoms (re-experiencing, avoidance, arousal) compared to cannabis abstinent participants. (Greer, Grob, & Halberstadt, 2014).

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Nabilone, a synthetic cannabinoid, has been shown to be effective in reducing PTSD symptoms including nightmares and insomnia. (Fraser, 2009; Cameron, Watson, & Robinson, 2014).

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Medical cannabis use has been associated with reductions in the use of opioids, alcohol, tobacco, and illicit substances. (Lucas et al, 2016)

# Tilray Patient Survey: Primary Illness & Symptoms

107 question survey available online in French and English for 2 weeks in July 2015, with 271 responses received.



## Primary Illness (n=271)

- 36% Chronic Pain
- 12% Arthritis
- 7% Psychiatric Disorder
- 7% PTSD
- 7% Insomnia
- 6% GI Disorder
- 5% Headache
- 4% Crohn's Disease
- 4% MS
- 3% Cancer/leukemia
- 2% Brain Injury

## Primary Symptoms (n=270)

- 73% Chronic pain
- 60% Stress
- 57% Insomnia
- 47% Depression
- 32% Headache
- 29% Appetite Loss
- 29% Nausea
- 27% Spasm
- 5% Memory Loss
- 4% Seizures
- 3% Intraocular Eye Pressure

# Substitution Effect, Tilray Patient Survey



Have you ever used cannabis as a substitute for:

Prescription drugs: 63%

Alcohol: 25%

Cigarettes/tobacco: 12%

Illicit drugs: 3%

# Substitution Effect; Prescription Drugs

## Substitution by Class of Prescription Drug (n=308)

Class	#	%
Oxy/OxyNeo/Percocet	43	14
Antidepressants (SSRIs/SNRIs)	36	12
Codeine Derivatives	35	11
Benzodiazepines	34	11
Hydromorphone/morphine	20	6
Sleep Aids	18	6
Other Pain (Tramadol/NSAIDS/other opiates)	64	20

Opioids are the pharmaceuticals most cited by patients who report substituting for prescription drugs, making up over 30% of the total drugs reported.

# Cannabis Substitution Effect

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According to Veterans Affairs Canada, significant increase in the use of medical cannabis by patients is paralleled by a nearly 30% decrease in the use of benzodiazapines and a 16% decrease in the use of opioids.

*(Mike Hager, Globe & Mail, June 6th, 2016)*

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## ***Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in the United States, 1999-2010***

States with medical cannabis laws had a 24.8% lower mean annual opioid overdose mortality rate (95%CI, -37.5% to -9.5%; P=.003) compared with states without medical cannabis laws.

*(Bachhuber et al. JAMA, 2014)*

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## ***Medical Marijuana Laws Reduce Prescription Medication Use In Medicare Part D.***

In medical cannabis states, the number of Medicare prescriptions to seniors dropped for drugs that treat pain, depression, anxiety, nausea, psychoses, seizures and sleep disorders. For pain, the annual number of daily doses prescribed per physician fell by more than 11%.

*(Bradford & Bradford, Health Affairs, 2016)*

# Medical Cannabis & PTSD - Protocol Design

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Randomized clinical trial

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Placebo-controlled with 2 active treatments

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Crossover design from Stage 1 to 2

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Triple-blinded

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42 participants

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2 treatment phases and 3 periods of cannabis abstinence

## **Primary Objective:**

To compare the independent effects of two active concentrations of vaporized cannabis to placebo on PTSD symptom severity measured by changes in CAPS-5 total scores during three weeks of ad-libitum self-administration during Stage 1 of the study protocol.

# Protocol Design Continued...

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**RESEARCH QUESTION:** Is 10% THC and/or 10% THC/10% CBD more effective than placebo cannabis in reducing symptoms of PTSD, anxiety, depression, and improving sleep and psychosocial functioning among participants?

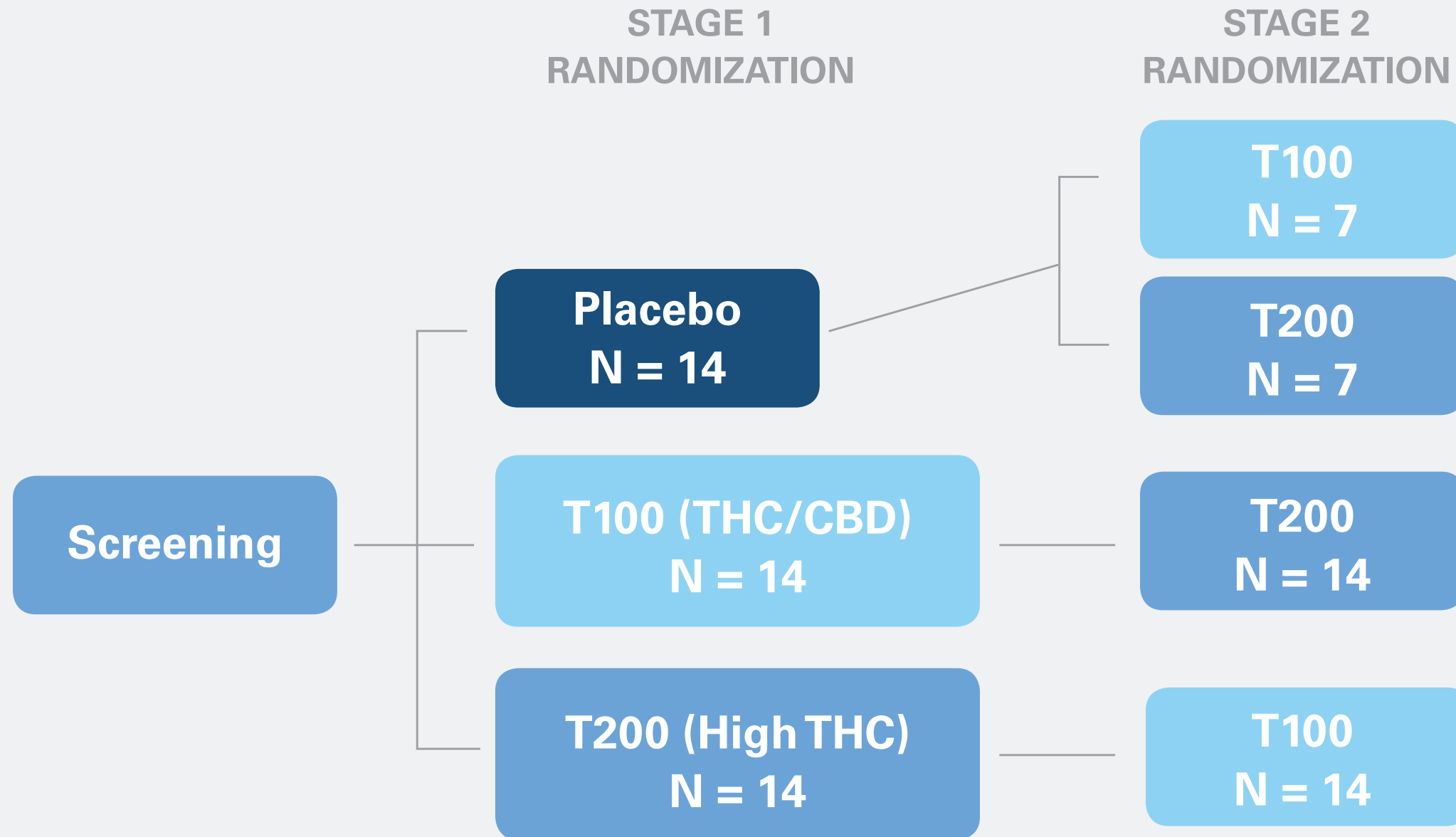
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**PROTOCOL VISIT SCHEDULE:** Initial abstinence of 2 weeks, followed by 3 weeks of placebo or active drug use in Stage 1, then 2 week wash-out, followed by 3 weeks on active drug in Stage 2, then 2 weeks wash-out, followed by a 6 month long-term follow up.

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**PROCEDURES:** During weekly site visits participants will be provided with 7 containers containing 2 grams of cannabis each, and can vaporize up to 2 grams per day, returning unused material so we can track actual dosages. Participants will use the Mighty Medic vaporizer, a Class 2 medical device in Canada.

# Randomization Design



# Significance

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This is the largest medical cannabis clinical trial to take place in Canada in over 30 years, and the first time Canadian clinical trial has been conducted to study the therapeutic potential of cannabis on a mental health condition.

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If cannabis proves to have therapeutic value in this population, it would add another tool to the very limited tool-belt physicians currently have in treating PTSD, and could help inform VAC and Canadian military policies re. medical cannabis and PTSD.

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Substitution effect: independent research and recent data from VAC suggests that an increased use of medical cannabis by vets with PTSD is also accompanied by a decline in the use of benzodiazapines and opioids.

—It may also be associated with a reduction in alcohol, tobacco and illicit drug use.

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No matter what the outcomes of this study, further research is necessary to better understand the mechanisms at work in regards to cannabis and PTSD.

# Maria — Tilray's First Patient

## Maria's Story

**Maria is a former Royal Canadian Mounted Police officer** who was injured in the line of duty, resulting in PTSD, chronic pain, a 60% loss of function in her left hand and the numbing symptoms of Raynaud's disease.



# QUESTIONS?

## **Philippe Lucas, MA, PhD Student**

VP of Patient Advocacy, Tilray  
Graduate Scholar, Centre for Addictions Research of BC

**[philippe@tilray.ca](mailto:philippe@tilray.ca)**



# Pharmacodynamic Effects of THC & CBD

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## The pharmacodynamic effects of THC include:

Analgesic  
Muscle relaxant  
Anti-emetic  
Appetite stimulating  
Psychoactive effects  
Immunomodulant

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## The pharmacodynamic effects of CBD include:

Analgesic  
Muscle Relaxant  
Anxiolytic  
Neuroprotective  
Anti-oxidant  
Anti-psychotic activity

# Summary of Visits

<b>SCREEN</b> ▼	Screen 1 and Screen 2 visits 2 week cessation period
<b>ENROLL</b> ▼	Enrollment of participant into study
<b>STAGE 1</b> ▼	Introductory Session 1 Visits 2–4
<b>CESSATION</b> ▼	Cessation 1 – start 2 week period of abstinence Stage 2 Baseline
<b>STAGE 2</b> ▼	Introductory Session 2 Visits 7–9
<b>CESSATION</b> ▼	Cessation 2 – start 2 week period of abstinence Long-term Follow-up Baseline (LTFU Baseline)
<b>STAGE 3</b> ▼	Optional: up to 8 weekly visits (Visit 11–18) if participants consent to participate If participants do not consent to participate, they will move into the LTFU phase of the study
<b>LTFU</b> ▼	LTFU visit – after 6 month period

# Post Traumatic Stress Disorder (PTSD)

PTSD is characterized by an inability to recover from a stress reaction following exposure to a traumatic event.

## Diagnosis requires specific types of trauma exposure:

1. Directly experiencing a traumatic event.
2. Witnessing an event occur to others.
3. Learning that an event occurred to someone else.
4. Exposure to aversive details of traumatic event(s) (e.g. first responders, police).

## Systems Include:

Avoidance—social isolation, anhedonia

Hyperarousal—anxiety, irritability, insomnia

Re-experiencing symptoms—dreams, memories

Negative alterations in cognition and mood

**\*Approximately 700,000 Canadians have been diagnosed with PTSD.**

# Questionnaires Completed at Visits

Some questionnaires and assessments will be administered by the investigator or delegated staff according to the protocol. These questionnaires will be completed on paper by the site staff and transcribed into REDCap.

These questionnaires include:

<b>Questionnaire</b>	<b>Reason for Assessment</b>
STOP-Bang Questionnaire	Eligibility criteria—Depression
CSSRS	Quality of life
GWB	Cannabis disorder
TLFB	Distress tolerance
SCID	Marijuana withdrawal
CAPS 5	Sleep quality
GAF	Anxiety and depression

# Additional Questionnaires

<b>Questionnaire</b>	<b>Reason for Assessment</b>
BD II	Eligibility criteria—Depression
WHO-QOL	Quality of life
CUDIT-R	Cannabis disorder
DTS	Distress tolerance
Behavioral Checklist	Marijuana withdrawal
PSQI	Sleep quality
IDAS	Anxiety and depression
CTS2S	Conflict tactics in relationships
IPF	Psychosocial functioning
PCL-5	PTSD
BAI	Anxiety
Bite	Irritability
LTFU	The effect of the study treatment

# Actigraphy



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Actigraphy is an objective assessment to measure sleep parameters and will be used over the course of the study to evaluate changes in sleep.

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To record sleep, the actigraphy device will be worn on the wrist like a watch to estimate sleep parameters.

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The measures that will be reported include: time to bed, time out of bed, latency, percentage of efficiency, total time in bed (min), total sleep time (min), wake after sleep onset, number of awakenings, average awakenings (min).

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Actigraphy has been well validated for the assessment of nighttime sleep parameters across age groups.

# The MMPR

## **The Marihuana for Medical Purposes Regulations (MMPR)**

The most significant change in medical cannabis access since 2001, the MMPR were implemented by Health Canada in December 2012, and went into full effect on April 1<sup>st</sup> 2014.

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Simplified/decentralized application process

NPs can prescribe (maybe)

Multiple Licensed Producers

Increased quality control

Increased strain/symptom awareness

# Current PTSD Treatments

## Psychotherapy:

Exposure-based interventions have the strongest evidence and include Cognitive Processing Therapy (CPT) and Prolonged Exposure Therapy (PET).

These therapies are considered standard psychosocial interventions for PTSD treatment but are associated with high rates of dropout and non-response.

A significant percentage of PTSD patients fail to respond adequately to established PTSD psychotherapies and treatments or respond in ways that are clinically inadequate.  
(Brady et al., 2000; Resick & Schnicke, 1992).

## Medications:

Selective serotonin reuptake inhibitors (SSRIs) and serotonin-and-norepinephrine reuptake inhibitors (SNRIs).

In Canada, Paroxetine, a selective serotonin reuptake inhibitor (SSRI), is approved as a PTSD treatment by Health Canada.