PAINWEEK

Cannabis or Cannabinoids: The Politics of Medical Marijuana

Douglas Gourlay MD, MSc, FRCP(c), DFASAM

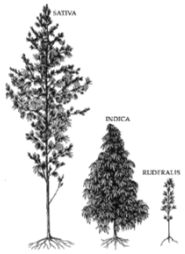
Disclosures

- Nothing to disclose

Objectives

- Review the pharmacology of marijuana and the impact of various routes of administration
- Examine some of the (possible) role(s) of cannabinoids in medicine
- Discuss some practical aspects of prescribing marijuana (herbal cannabis)
- Identify clinical traps

Cannabis Family Photo



PainWeek

4

The "New" Cannabis

….woodsy with a hint of mustiness, and as always with just a hint of pine

PainWeek

5

Dr. Louis Hugo Francescutti, Past CMA President

- "It was a court that said we believe there's benefit and patients should have access to it", regarding the 2000 Ontario Ruling leading to Ottawa's initial marijuana regulations
  - "So it was the courts that quite frankly put us in this mess…and trust me, we are in a mess."
- "You can rest assured," says Francescutti "there's going to be more than one physician who's going to get disciplined over this."

PainWeek

6

Pharmacology

- Cannabis is not one drug, it's a mixture of drugs
  - Primarily interested in CBD and THC
  - Pleasurable effects include
    - Mild euphoria and relaxation
    - Heightened sensory perception
      - Brighter colors
      - Stronger smells
      - Increased appetite ("the munchies")
  - Distortion of time perception
    - Perceived time goes faster than clock time

PainWeek

7

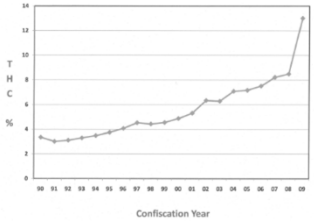
Cannabis—Yesterday and Today

- Cannabis studies done 20 years ago describe a much lower potency drug than today
  - Genetic hybridization/THC optimization
  - Cannabinoid derivatives/synthetics
- No longer just "joints and brownies"
  - Cannabis oil; cannabis butter; blunts; spiffs….

PainWeek

8

Average Potency Confiscated THC %

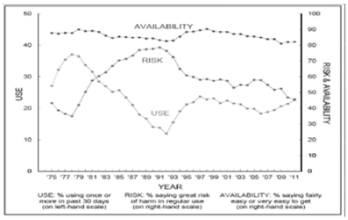


The University of Mississippi Potency Monitoring Project

PainWeek

9

Adolescence



Monitoringthefuture.org

PainWeek

10

Pharmacology

- Herbal cannabis contains over 500 compounds—in excess of 100 cannabinoids
  - Pharmacology is largely unknown but most potent is Δ-9 THC
  - Δ-8 THC, cannabinol, cannabidiol have additive, synergistic, and even antagonist activity wrt Δ-9 THC
  - Cannabis and tobacco are similarly constituted, except for nicotine

PainWeek

Savage, Seddon et al. Cannabis in Pain Treatment: Clinical and Research Considerations, J of Pain. 17(6), 2016 pp 654-658

11

Pharmacokinetics

- ~50% of the THC in a joint is inhaled through smoke
  - Pulmonary absorption is nearly 100%
    - Onset within seconds
  - Bioavailability of oral THC is ~25-30% of the pulmonary dose
    - Extensive 1st pass effect in the liver
    - Delayed onset (0.5-2hrs) with much prolonged duration due to ongoing absorption from the gut

PainWeek

12

Pharmacokinetics (cont'd)

- Due to high lipid solubility, cannabinoids accumulate in fatty tissue
  - Elimination $t_{1/2}$ is ~7 days
- In the brain, cannabinoids are differentially distributed
  - Highest concentrations in neocortical, limbic, sensory, and motor areas

PAINWEEK

13

Metabolism

- Primarily hepatic, with major metabolite as 11-hydroxy-THC (biologically active)
  - Excretion is ~25% urine, the rest gut (65%)
- This all results in an unpredictable relationship between plasma or urine conc and degree of cannabinoid-induced intoxication

PAINWEEK

14

Pharmacology

- 1992, first endogenous ligand for CB receptors was discovered
  - Anandamide (from Sanskrit for "bliss")
    - Structurally related to prostaglandins not THC
      - Effects are similar to THC
    - Appear to behave as neurotransmitters affecting cAMP formation and Ca^{2+} and K^{+} ion transport
  - THC has been shown to increase dopamine release (via permissive role of opioid pathway)

PAINWEEK

15

Sites of Action

- The endocannabinoid system is distributed throughout the brain and spinal cord
  - CB-1 receptors are concentrated in the hippocampus, association cortices, basal ganglia, cerebellum, and spinal cord (especially dorsal root ganglia)
  - CB-2 receptors are found in the periphery including lymph tissue as well as in lower amounts in the brain including the periaqueductal gray
- Activation of these receptors results in physiologic responses that would be expected from these regions

PAINWEEK

Koppel BS, Brust JCM, Fife T, et al. Systematic Review: Efficacy and safety of medical marijuana in selected neurologic disorders Neurology 2014;82:1556-1563

16

Sites of Action (cont'd)

- Examples of such responses include: a feeling of well-being, psychosis, diminished locomotor functioning, impaired memory/cognition, *ANTINOCEPTION, SPASTICITY REDUCING, SLEEP PROMOTING*, and antiemetic action
  - Receptor activation inhibits adenylate cyclase and subsequently the release of multiple neurotransmitters is inhibited when neuronal excitation is present
  - These neurotransmitters include glutamate, acetylcholine and dopamine
- Other neuronal networks may be modulated by endocannabinoids through indirect effects on opiate, n-methyl d-aspartate (NMDA), and gamma amino butyric acid (GABA) receptors

PAINWEEK

Koppel BS, Brust JCM, Fife T, et al. Systematic Review: Efficacy and safety of medical marijuana in selected neurologic disorders Neurology 2014;82:1556-1563

17

Important Additional Considerations Regarding Medical Marijuana for CNS Disorders

- The concentration of THC as well as the ratio of THC to CBD in specific formulations is what limits (or not) THC's psychoactive effects
- Key examples: Dronabinol: 2.5mg THC; Nabilone: 1mg (CBD); Sativex® 1:1 ratio of THC 2.7mg/CBD mg/spray; **Smoked marijuana**: 4% THC (this number is rising)

Koppel BS, Brust JCM, Fife T, et al. Systematic Review: Efficacy and safety of medical marijuana in selected neurologic disorders Neurology 2014;82:1556-1563

PAINWEEK

18

Effects of Cannabis

- Short term
  - Effect on mood is *usually* euphorigenic
    - 2.5mg smoked gives a feeling of intoxication, decreased anxiety, tension and increased sociability
      - Duration of action is typically 2hrs or more (dose related)
    - Dysphoric effects include anxiety, aggravation and frank psychosis
  - Effects on perception
    - Heightened sensitivity, spatial and time distortion
    - Perceived time goes faster than clock time

PAINWEEK

19

Effects of Cannabis (cont'd)

- Effects on cognition and psychomotor performance
  - Similar to alcohol and benzodiazepines i.e. slowing of reaction time, motor coordination, specific defects in short-term memory, impaired concentration and complex task performance
    - All effects are *at least* additive with other CNS depressants
  - Tolerance is neither complete nor predictable

PAINWEEK

20

Cannabis and Driving

- Cannabis impairs road-driving performance
  - Numerous studies link cannabis with increased motor vehicle accidents
  - In the UK, USA, Australia, New Zealand, and many European countries, cannabis is the most common drug (apart from EtOH) detected in drivers involved in fatal accidents or stopped for impaired driving

PAINWEEK

21

Chronic Effects of Cannabis Use

- As usual, risk is multifactorial
  - Unfortunately, the risk in adolescence appears to be long term and dose-related
  - Some risk appear to be genetically mediated
    - Risk is not equal for all persons
  - Addiction
  - Psychiatric comorbidities
  - Schizophrenia—marijuana link

PainWeek

22

Therapeutic Benefits of Cannabinoids

- Importance of separating the molecule from the route of administration
- Clearly beneficial
  - Chemo induced nausea
  - HIV-associated anorexia and wasting
  - Refractory glaucoma
  - ? Neuropathic pain and spasm of multiple sclerosis (subjective—YES; objective—NO)

PainWeek

23

THC/CBD Potential Benefits

- THC is said to have analgesic, anti-spasmodic, anti-tremor, anti-inflammatory, appetite stimulant, and anti-emetic properties, whilst…
- CBD has anti-inflammatory, anticonvulsant, anti-psychotic, anti-oxidant, neuroprotective, and immunomodulatory effects
  - CBD is not intoxicating and indeed it has been postulated that the presence of CBD in cannabis may alleviate some of the potentially unwanted side-effects of THC

PainWeek

http://www.gwpharm.com/types-compounds.aspx

24

Practical Aspects of *Prescribing* Herbal Cannabis

- No standardization of dose
  - Concentration of product is highly variable
  - Route of administration (smoking vs oral) leads to vastly different serum levels and effects
- No clear *indications* or *contraindications* to guide the prescriber
- No *practical* means of controlling the amount of drug used

PainWeek

25

Legal Liability

- Direct liability
  - Complaints to college if you do or don't complete the forms
  - *Iatrogenic harm* caused by your prescription of cannabis (to the patient)
- Third party liability
  - If someone else comes to harm as a result of actions of your patient using prescribed/recommended cannabis

PainWeek

26

Occupational Health and Safety

- Not a lot of 'hard and fast' data
  - In the absence facts, 'rules' will still be created and enforced
- Things to consider:
  - Having a 'medical certificate' will NOT protect employee from 'dismissal for cause' based on drug use
  - 'Driving while impaired' and similar will be prosecuted with or without medical excuse

PainWeek

27

So, what can you do?

- Unless you can competently discuss the pro/con of herbal cannabis, including indications and contraindications for use i.e. provide informed consent…. you would be wise to consider carefully any decision to prescribe/recommend
  - Until that time….approved pharmaceutical options might be your best choice (with careful documentation of your thoughts and actions)
    - Or…..recommendation that the patient seek evaluation at one of the many cannabis clinics popping up around the country

PAINWEEK

28

Clinical Traps

- "But it's the only thing that works for me!"
  - Most difficult argument to defuse
    - But, if cocaine was the only thing that worked for my nasal stuffiness, would you prescribe?
  - For the most part, those advancing smoked cannabis as the "gold standard" are long-standing pot smokers
    - You can recommend "harm reduction" methods such as vaporizing aka "vaping" rather than combusted cannabis

PAINWEEK

29

Clinical Traps (cont'd)

- Once you legitimize the presence of the analyte in the urine, you've lost the ability to monitor use/misuse/diversion
  - This can have serious implications for "return to work" requirements, 3rd party advocacy etc
    - Disability claims
    - Child Protective Services
    - Criminal justice (probation/parole)
    - Operation of a motor vehicle

PAINWEEK

30

Clinical Traps (cont'd)

- "Well, I'm still going to use. If you don't prescribe for me….I'll just continue to use illicitly. If I go to jail, it's on you!"
  - When a patient holds you hostage with threats, you (and the patient) are on very shaky therapeutic grounds
    - Would you prescribe opioids under these terms?
  - Consider having a 3rd party in the room for these discussions—DOCUMENT EVERYTHING

PAINWEEK

31

Conclusion

- Dried cannabis is NOT a medication in any traditional sense of the word
  - That doesn't mean cannabinoids have no legitimate indication as therapeutic agents
    - But smoking *anything* for your health in 2017 is oxymoronic: proceed with care!
- Canada's Medical Marijuana Program is about political policy, not about resolving an unmet medical need

PAINWEEK

32

Resources

- Medical Marijuana (aka Marihuana)
  - Act repealed March 31st, 2014 - CANADA
- College of Family Physicians of Canada
  - http://www.cfpc.ca/uploadedFiles/Health_Policy/CFPC_Policy_Papers_and_Endorsements/CFPC_Policy_Papers/Medical%20Marijuana%20Position%20Statement%20CFPC.pdf
- CMPA April 2014 update
  - https://oplfrpd5.cmpa-acpm.ca/-/medical-marijuana-new-regulations-and-transition-period
- Cannabis in Pain Treatment: Clinical and Research Considerations
  - Savage, Seddon et al. J of Pain 17(6) 2016: pp654-668
- Should doctors prescribe cannabinoids?
  - www.bmj.com/content/348/bmj.g2737
- dgourlay@cogeco.ca (Dr Douglas Gourlay)

PAINWEEK

33