Cannabis or Cannabinoids: The Politics of Medical Marijuana
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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
- Explore some practical aspects of prescribing marijuana (herbal cannabis)
- Clinical traps

Cannabis Family Photo
The “New” Cannabis

AK-47

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

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.”
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

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...
Average Potency Confiscated THC %

The University of Mississippi Potency Monitoring Project

Adolescence

Monitoringthefuture.org
Pharmacology

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

Pharmacokinetics

- $\sim50\%$ of the THC in a joint is inhaled through smoke
  - Pulmonary absorption is nearly 100%
    - Onset within seconds
  - Bioavailability of oral THC is $\sim25\%$ to $30\%$ of the pulmonary dose
    - Extensive 1st pass effect in the liver
    - Delayed onset (0.5-2 hours) with much prolonged duration due to ongoing absorption from the gut

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

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

Metabolism

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

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

Sites of Action (cont’d)

- Examples of such responses include: a feeling of well-being, psychosis, diminished locomotor functioning, impaired memory/cognition, **ANTINOCICEPTION, 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


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: 100mg CBD
  - Sativex® 1:1 ratio of THC 2.7mg/CBD mg/spray
  - Smoked marijuana: 4% THC (this number is rising)

Effects of Cannabis

- **Short term**
  - Effect on mood is *usually* euphoric
    - 2.5 mg smoked gives a feeling of intoxication; decreased anxiety and tension; and increased sociability
      - Duration of action is typically 2 hours 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

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
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

Chronic Effects of Cannabis Use

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

THC/CBD Potential Benefits

- THC is said to have analgesic, antispasmodic, antitremor, anti-inflammatory, appetite stimulant, and antiemetic properties, whilst...

- CBD has anti-inflammatory, anticonvulsant, antipsychotic, antioxidant, 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

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

**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)
- 3rd party liability
  - If someone else comes to harm as a result of actions of your patient using prescribed/recommended cannabis
The College of Family Physicians of Canada

- Medical Marijuana, February 2013
- Health Canada should explicitly state the indications, precautions and contraindications for medical marijuana, as it does with all other therapeutic medications. In making these determinations, Health Canada should consider the following factors:

  - (a) No prescribed medication uses smoke (combustion of herbal material) as a delivery system. Smoke is a hazardous delivery system, because (a) psychoactive ingredients reach the CNS much faster than other routes, causing intoxication; and (b) smoke contains hundreds of chemicals that are potentially carcinogenic or harmful to the heart or other organs. Similarly, there is no evidence for the safety or efficacy of oral ingestion of herbal cannabis.

The College of Family Physicians of Canada (cont’d)

- (b) The active ingredient of cannabis, or synthetic cannabinoids, THC, can already be prescribed as an oral capsule (nabilone) and as an inhaled spray (Sativex). Use of nabilone or Sativex for chronic pain is off label: nabilone has the indication for “treatment of refractory nausea and vomiting associated with cancer chemotherapy” while Sativex’s indication is “Spasticity or neuropathic pain associated with multiple sclerosis, cancer pain”.

- (c) The evidence supporting the analgesic effectiveness of cannabis is weak. Controlled trials were of short duration and had small sample sizes and incomplete outcome measures. Smoked cannabis was compared against placebo, not against other cannabis formulations or standard analgesics. Many subjects in the trials were regular cannabis smokers.
The College of Family Physicians of Canada (cont’d)

- Smoked cannabis poses serious risks, particularly in young people. These risks include psychosis, cannabis addiction, depression, poor school or work performance, motor vehicle accidents, and neurodevelopmental effects in children of pregnant cannabis smokers. Evidence regarding carcinogenesis is conflicting, but it is known that cannabis smoke contains carcinogens.

So, what can you do?

- Unless you can competently discuss the pro/con of herbal cannabis, including indications and contraindications for use, ie, 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
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

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
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

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 2016 is oxymoronic: proceed with care!
  • Canada’s Medical Marijuana Program is about political policy, not about resolving an unmet medical need
Resources

- Medical Marijuana (aka Marihuana)
  - Act repealed March 31st, 2014
- College of Family Physicians of Canada
- CMPA April 2014 update
- 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
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