

Cultural Learnings of Cannabis Research for Make Benefit Glorious Nation: The Trials and Tribulations of Cannabis Research in Canada



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Pharmacology

> 60 cannabinoids (THC, CBD, CBN)

Concentration of cannabinoids varies depending on growing conditions, plant genetics, and processing after harvest

THC liposoluble: Limits the possible formulations of cannabis preparations

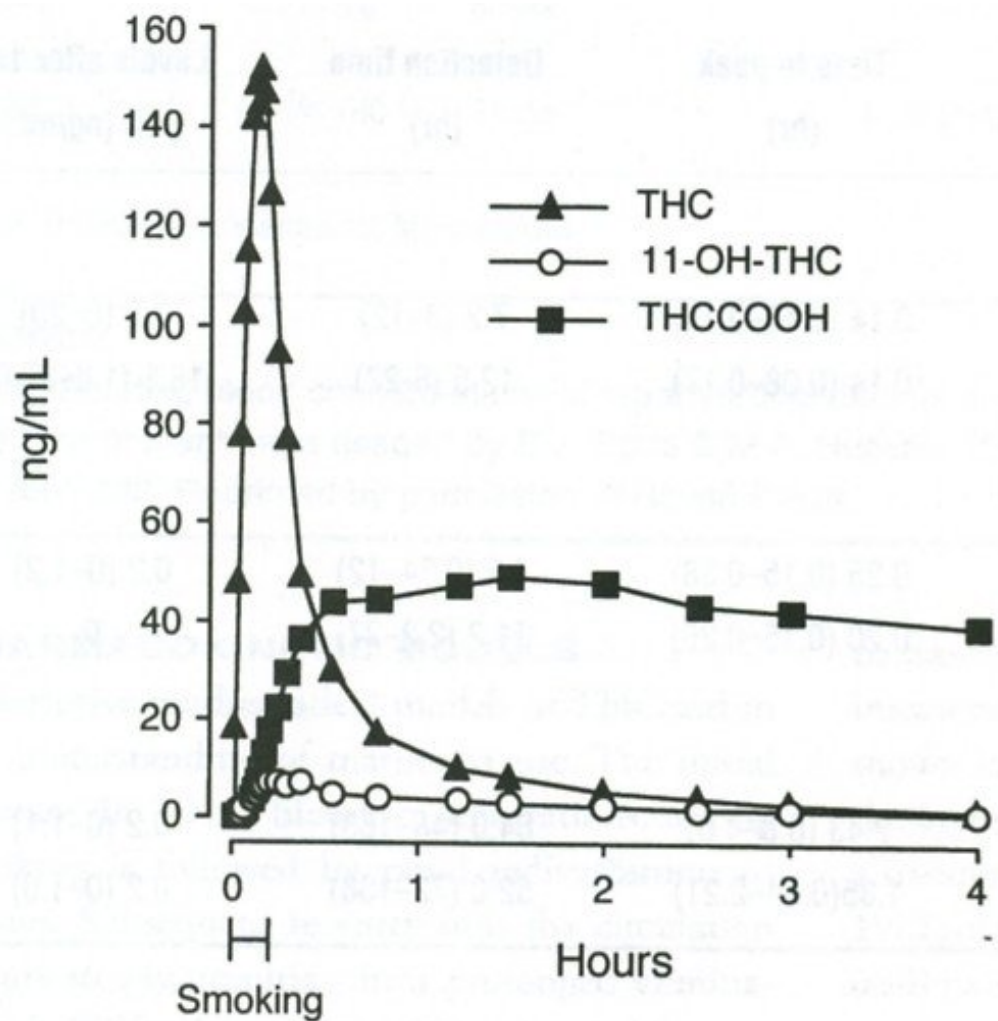
Route of administration determines pharmacokinetics:

- When smoked, THC is absorbed quickly into the bloodstream
- When taken by mouth, onset of effects is slower and last longer

After smoking, blood levels of THC fall significantly within minutes (1h later, 5-10% of peak level)

Rapid clearance from blood largely due to redistribution to other tissues, especially fatty tissues

Mean plasma THC concentration after smoking a single 3.55% THC joint





1st UCSF study: Safety of cannabinoids in HIV

RCT to assess the safety of cannabinoids in HIV

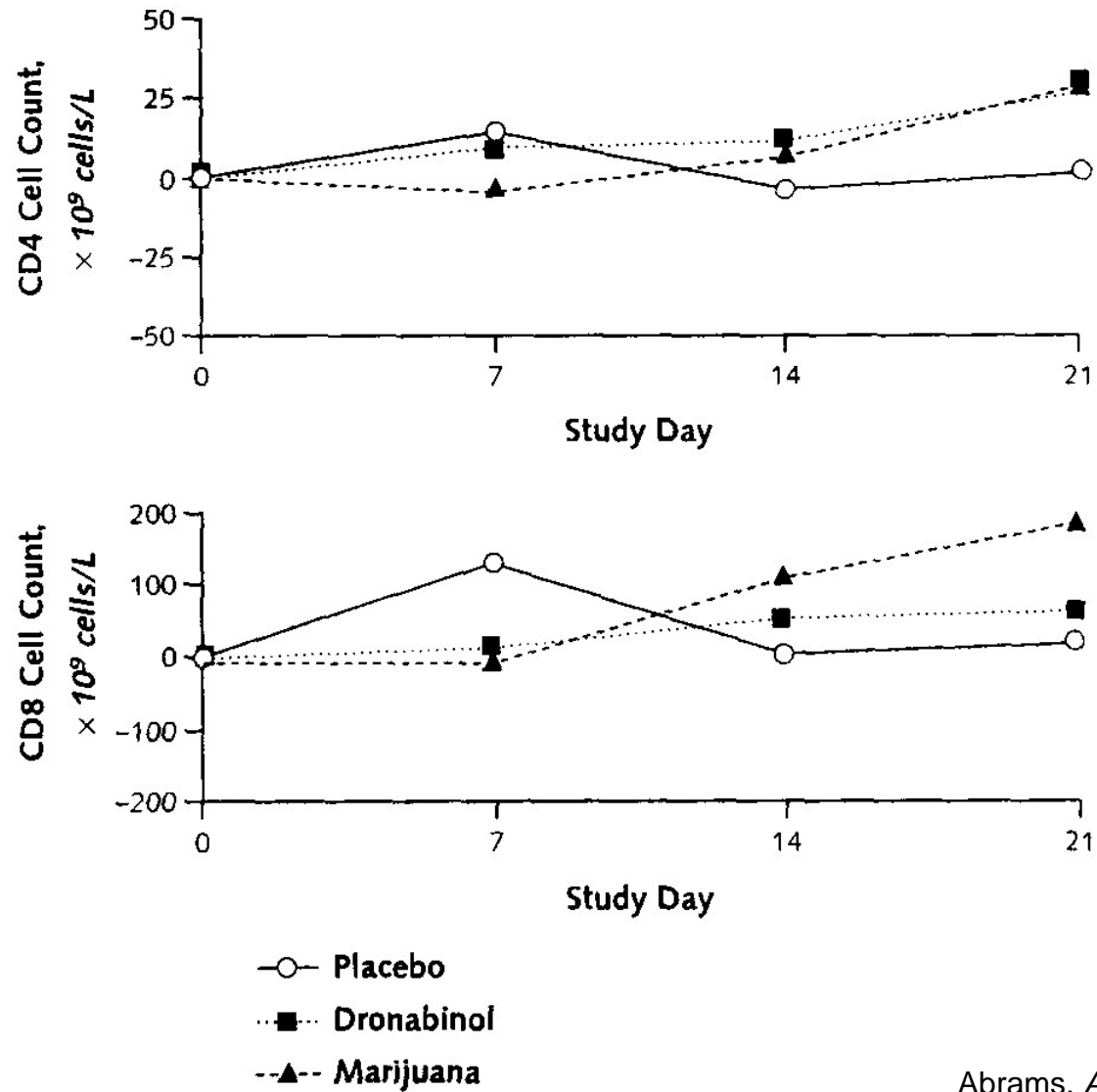
67 PHAs on antiretroviral regimen including either indinavir or nelfinavir were randomized to receive either smoked cannabis, oral THC (Marinol), or placebo tid before meals

The study found no significant changes in viral load and CD4/CD8 counts over 21 days.

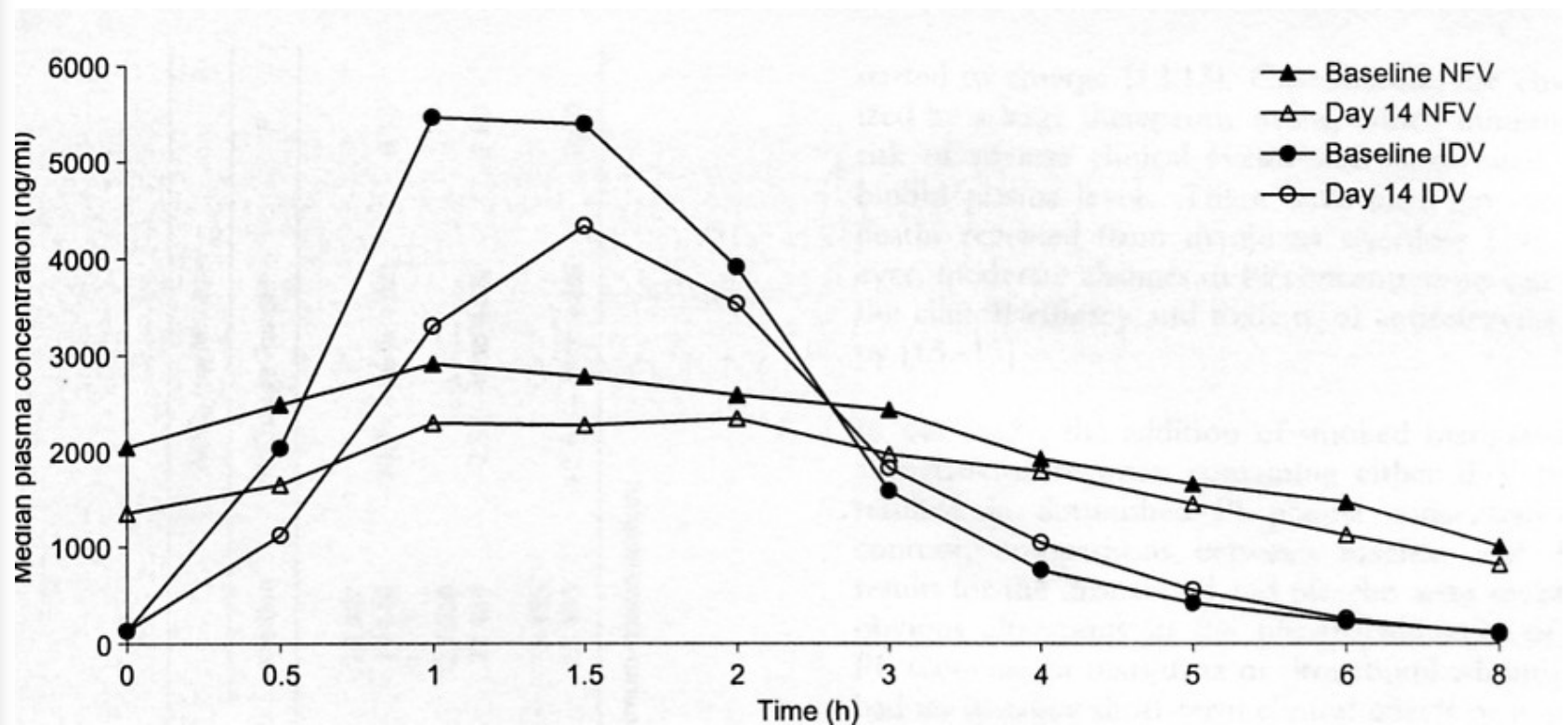
However, it found a 14% reduction in indinavir levels and a 10% reduction in nelfinavir levels in the cannabis group at day 14 compared to baseline

It also found a significant increase in weight for both the cannabis and Marinol groups. However, most of the weight gained was fat mass

Median change in CD4/CD8 counts by group



Median plasma concentrations over dosing interval of IDV and NFV at baseline and 14 days for the cannabis group





2nd UCSF study: Effects of cannabis on neuropathic pain in HIV

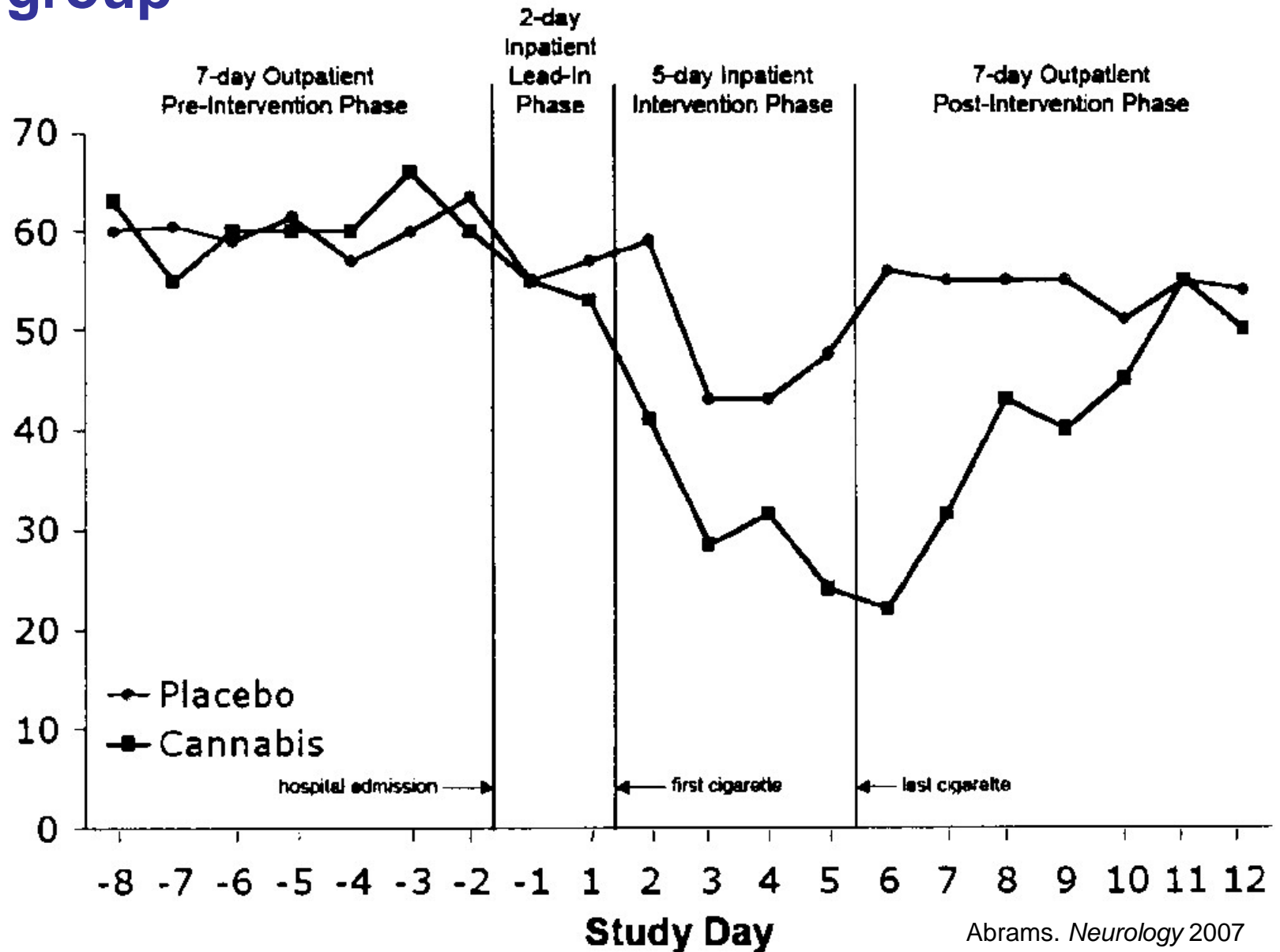
RCT to determine the effects of smoked cannabis on HIV-associated neuropathic pain

55 PHAs randomized to smoke either cannabis or placebo tid for 5 days in an inpatient setting

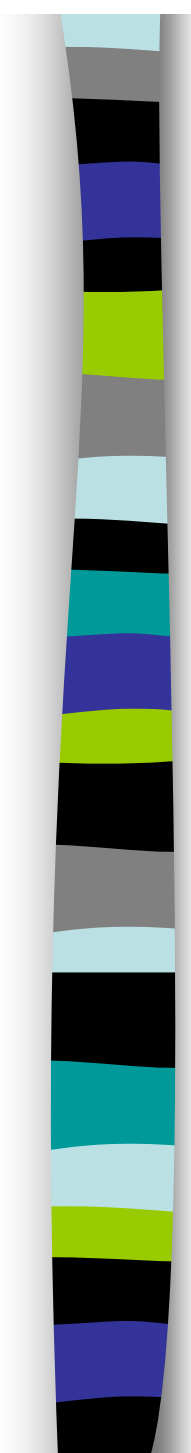
Greater than a 30% reduction in pain was reported by 52% in the cannabis group and by 24% in the placebo group (Difference=28%, $p=.04$)

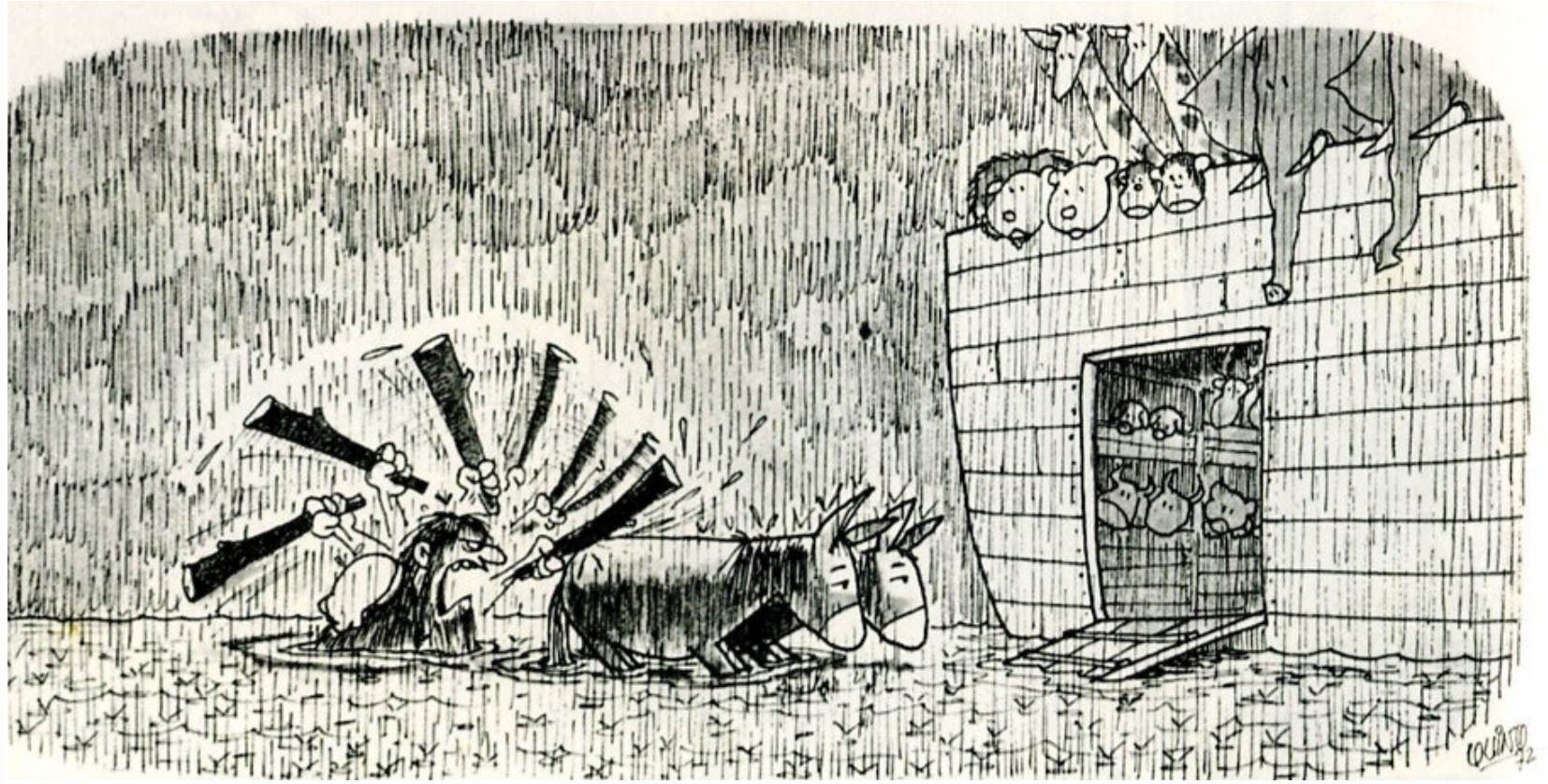
Smoked cannabis reduced daily pain by 34% vs a placebo reduction of 17% ($p=.03$)

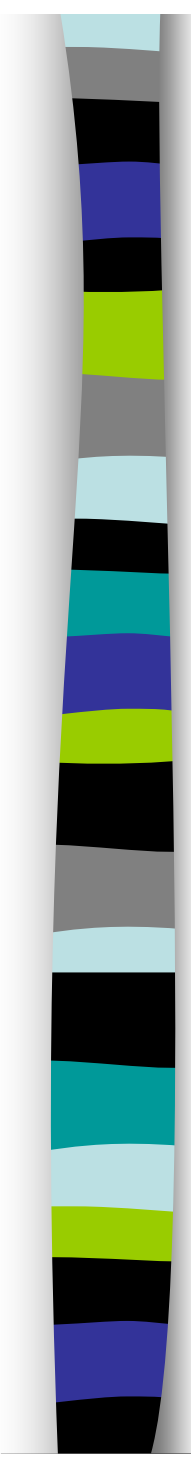
Time course of median daily pain ratings by group



Study milestones

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- 1999** Alan Rock announces the Medical MJ Research Program (MMRP)
- 2001** Designed a randomized cross-over trial looking at the effects of smoked cannabis on appetite stimulation in HIV
Obtained REB approval from SMH, IND approval from Health Canada, and a license for a pipe as a delivery system from the MDB
- 2002** Obtained research-grade cannabis from NIDA (US)
Pilot tested the delivery mechanism and blinding
Meetings with RCMP, Toronto Police Service and Justice Department
- 2003** MMRP withdraws funding
- 2003-2004** Explored alternative funding mechanisms with Health Canada (contract, contribution agreement)
- 2005** Obtained funding from OHTN for a dose-titration study
- 2006** Redesigned the study to turn it into a RCT
Smoke-Free Ontario Act comes into effect, closing the smoking room built for the study
- 2007** MMRP is cancelled





Study Population: Naïve versus Experienced Users

Ethical concerns about introducing cannabis to patients who have never been exposed to cannabis before

Practical issues related to cannabis administration in naïve users: May require training to inhale properly

No reliable data on acceptability of smoked cannabis to naïve users or experienced users who have had negative experiences or lack of symptom relief with cannabis

Selection bias: Experienced users would be more likely to believe in the efficacy of cannabis for therapeutic purposes

- Exclusion of participants with recent exposure (30 days)
- Assessment of cannabis use history & role of expectancies



Blinding

Although placebo available, blinding difficult

- Different physical characteristics (color, texture) for materials containing different THC concentrations, in particular placebo cannabis
- Experienced users may detect placebo by lack of psychoactive effects

In inpatient studies, masking physical characteristics possible by using cigarette holder and closing other end (joints) and wrapping unit doses in rolling paper (pipe)

Blinding is even more difficult in outpatient studies and in studies targeting long-term outcomes



Dosing

No good data on appropriate doses

Smoking behaviour and dose control

- Puff and inhalation volume changes with phase of smoking
- As the joint length shortens, the concentration of THC increases
- Partial control over drug dose delivered

Two strategies to manipulate dose delivered:

- Use same THC content but alter number of puffs
- Use material of differing THC content while maintaining amount of smoke delivered constant

Two methods have been used:

- Whole joint (8 puffs) as standard dose
- Half joint (4 puffs)
- Potential alternative is to allow dose titration

Dose delivery problematic because of individual differences in smoking behavior



Delivery: Joint versus Pipe

More appropriate to quantify the amount of herbal material actually consumed by administering small doses (25mg) using a pipe

Also offers better estimation of dose requirements in pharmacokinetic studies because less THC is lost in side-stream smoke

Proportion of paper to cannabis may result in unacceptable 'harshness' to smoker

Equivalent THC content in unit doses requires using finely ground material that may affect burning properties of material



Other Challenges

Choice of outcome

- Appetite stimulation, nausea suppression and pain relief are reasonable targets. Problematic if blinding difficult
- Objective outcomes (e.g. weight gain, body composition) more desirable but longer to observe

Use of “street” cannabis difficult to control and monitor

- Assay development to detect cannabis use outside protocol requires testing street material in volunteers (based on low CBD concentration in research material). No legal framework available



Legal issues: Criminal Liability

Participants are legally protected as long as the cannabis is provided by an investigator who holds an exemption by the federal government under the CDSA

Participants to carry a letter at all times

Participants will not carry more than 5 grams at a time

Legal protection does not extend outside Canada

We have arranged for legal counsel to be on call

We will arrange meetings with law enforcement agencies to educate them about the research

- RCMP, Toronto Police Service, Department of Justice



Legal issues: Civil Liability

Claims by participants for indemnity in the event that they are subjected to criminal prosecution

- This type of risk is virtually eliminated

Claims by participants re: adverse health consequences of cannabis use

- This type of risk can be reduced by documenting the potential adverse health consequences in the consent form

Claims by third parties adversely affected by the conduct of participants while under the influence of cannabis

- This type of claim can never be completely eliminated
- It can be minimized by banning driving and providing a TTC Metropass