Should Marijuana be a Medical Option?

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Presentation to the National Association of Boards of Pharmacy

December 3, 2009

Why do we care about the FDA process?

- Provisions developed over the past 100 years to protect patient health and safety
  - promote quality, safety and efficacy of medications;
  - supported by all major medical organizations
- Extensive preclinical and clinical testing provides a robust body of risk/benefit and pharmacological data
  - physicians need this to inform their prescribing decisions
- Registration/inspection ensures that the manufacturing process is conducted in accordance with validated quality control tools
- Promotional activities of manufacturers limited
- Products prescribed/dispensed under the supervision of licensed health care providers, e.g., physicians, pharmacists

Modern Regulatory Approval Requirements: Quality, Safety & Efficacy

- Quality
  - Product Composition
  - Characterization
  - Quantification of components
  - Standardization/Consistency
  - Stability/Storage
- Safety
  - Animal data, including:
    - Carcinogenicity
    - Reproductive toxicology
    - Chronic toxicology
    - Genotoxicology
    - Safety pharmacology
  - Clinical data
    - Several hundred patient-years of data required
    - Reports of all adverse events (mild/moderate/severe – related and unrelated)
    - Immediate regulatory notification of serious adverse events
- Efficacy
  - Multiple Phase II & Phase III placebo-controlled clinical trials for each target clinical indication

Does "medical marijuana" fit into the FDA paradigm?

- Composition (% of THC) of herbal cannabis varies significantly
  - depends on strains, cultivation and storage, etc.
- North American cannabis bred to exhibit (only) high levels of THC
  - no meaningful levels of other cannabinoids such as CBD
- Delivery systems (smoked/vaporized, baked goods, teas) do not provide a standardized dose
  - smoking delivers harmful combustion products to the lungs
  - Vaporization does not completely eliminate PAHs
- Contamination with microbes, heavy metal, and pesticides a real possibility

How does “medical marijuana” currently fit into the FDA paradigm? con’t

- Distribution does not take place within regulated supply chain for pharmaceuticals
  - “collectives” and “cooperatives”
- No collection of adverse event or efficacy data
  - impossible to know who is really benefiting or being harmed
- Medical advice being given by untrained and unlicensed individuals
  - broad efficacy claims
  - often no meaningful physician supervision
  - no labeling with risk information or instructions for use
- Patients cannot obtain health insurance coverage

What would it take for a cannabis product to secure FDA approval?

- Herbal material grown by clones under rigorous conditions, ideally computer controlled greenhouses, to produce standardized starting materials
  - Under international policies of last 85 years, US imports, rather than cultivates, psychoactive herbal material and manufactures finished products in US
- Need to incorporate **an extract** ("Botanical Drug Substance") into an appropriate delivery system;
  - No precedent for administering **any** crude herbal material in a manner that reliably achieves a reproducible dose, produces no carcinogens

FDA approval con't

- Sponsor must manufacture and test product in accordance with FDA "Guidance for Industry: Botanical Drug Products"
  - Guidance allows some leniency in early research; by Phase 3 /NDA, all NCE standards must be met
  - Blinded, placebo-controlled large clinical studies must examine specific medical condition in specific population
  - Sponsor must conduct abuse liability testing and prepare risk management plan

What About the DEA?

- DEA must register clinical and preclinical research sites and importer/manufacturer
- After NDA, DEA must reschedule product
  - FDA approval satisfies “currently acceptable medical use in the US” **for that product**

Should Cannabis be Rescheduled?

- If a cannabis-derived product were FDA approved, must cannabis itself be moved to Schedule II, like opium and cocaine?
- Conversely, must cannabis be rescheduled in order for such a product to reach the market?
- Probably not. Split scheduling appears to be possible.
  - Marinol (Schedule III) and Cesamet (Schedule II) vs. THC (Schedule I);
  - Xyrem (Schedule III) vs. GHB (Schedule I)

What Would Rescheduling Achieve?

- FDA does not approve bulk substances/active ingredients for direct prescriptive use
- **Even if "cannabis" itself were moved to Schedule II, a specific cannabis or cannabis-based product would need FDA approval to be available by prescription**
- Might at most speed up the obtaining of initial research registrations

Giving Cannabis a Free Pass = ?

- By creating an exception for cannabis, we are preventing the development of Q, S & E data that would allow it to become broadly accepted as a true medication
- The vast majority of patients want a product that is standardized by composition and dose and about which their physicians can offer meaningful advice

More Research Needed: Formulation is Important

- Cannabis plant is the unique source of cannabinoids
- Over 60 cannabinoids in total, each with their own—often complementary—pharmacology, especially CBD
- Also other pharmacologically active components, e.g., terpenes, flavonoids

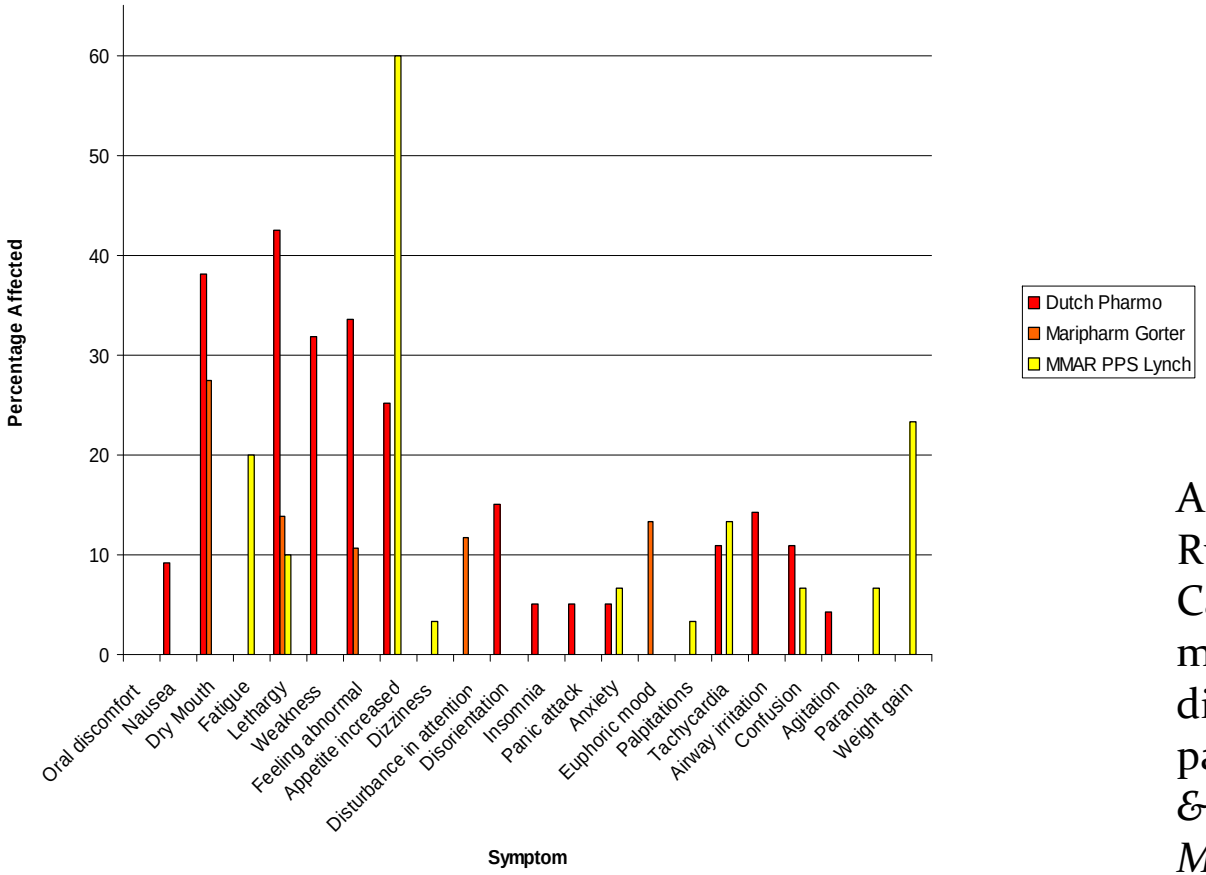
There's More Than THC!

- Cannabis used centuries ago would have involved a 1:1 CBD:THC ratio
- THC (tetrahydrocannabinol):
  - is analgesic, anti-spasmodic, anti-tremor, anti-inflammatory, appetite stimulant, anti-emetic
- CBD (cannabidiol):
  - does not bind to CB1 cannabinoid receptor, but does bind to other receptors in the body;
  - is anti-inflammatory, analgesic, anti-convulsant, anti-psychotic, anti-oxidant, neuroprotective;
  - reduces the negative effects of THC;
  - has been bred out of modern herbal cannabis!

The Delivery System is Also Important

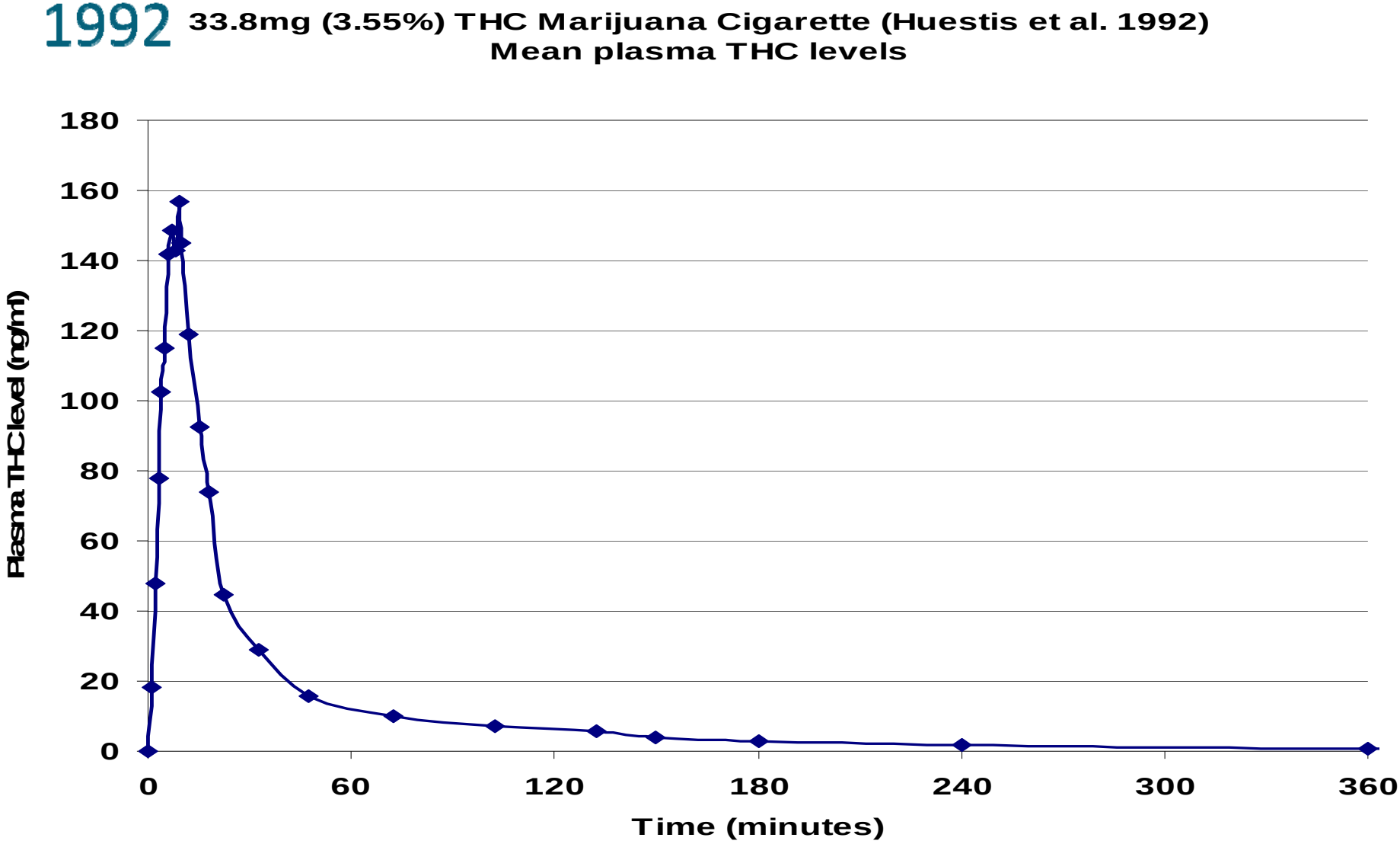
- THC-containing cannabinoid products have a narrow therapeutic window
- How to provide and maintain therapeutic blood and tissue levels of key cannabinoid components without incurring unacceptable side effects

AE of Standardized Smoked Medicinal Cannabis



Adapted from Russo, E.B. 2008. Cannabinoids in management of difficult to control pain. *Therapeutics & Clinical Risk Management* 4(1):245-259.

THC Levels from Smoked Cannabis (Huestis et al. 1992



Cannabinoid Therapeutic Window: Challenges

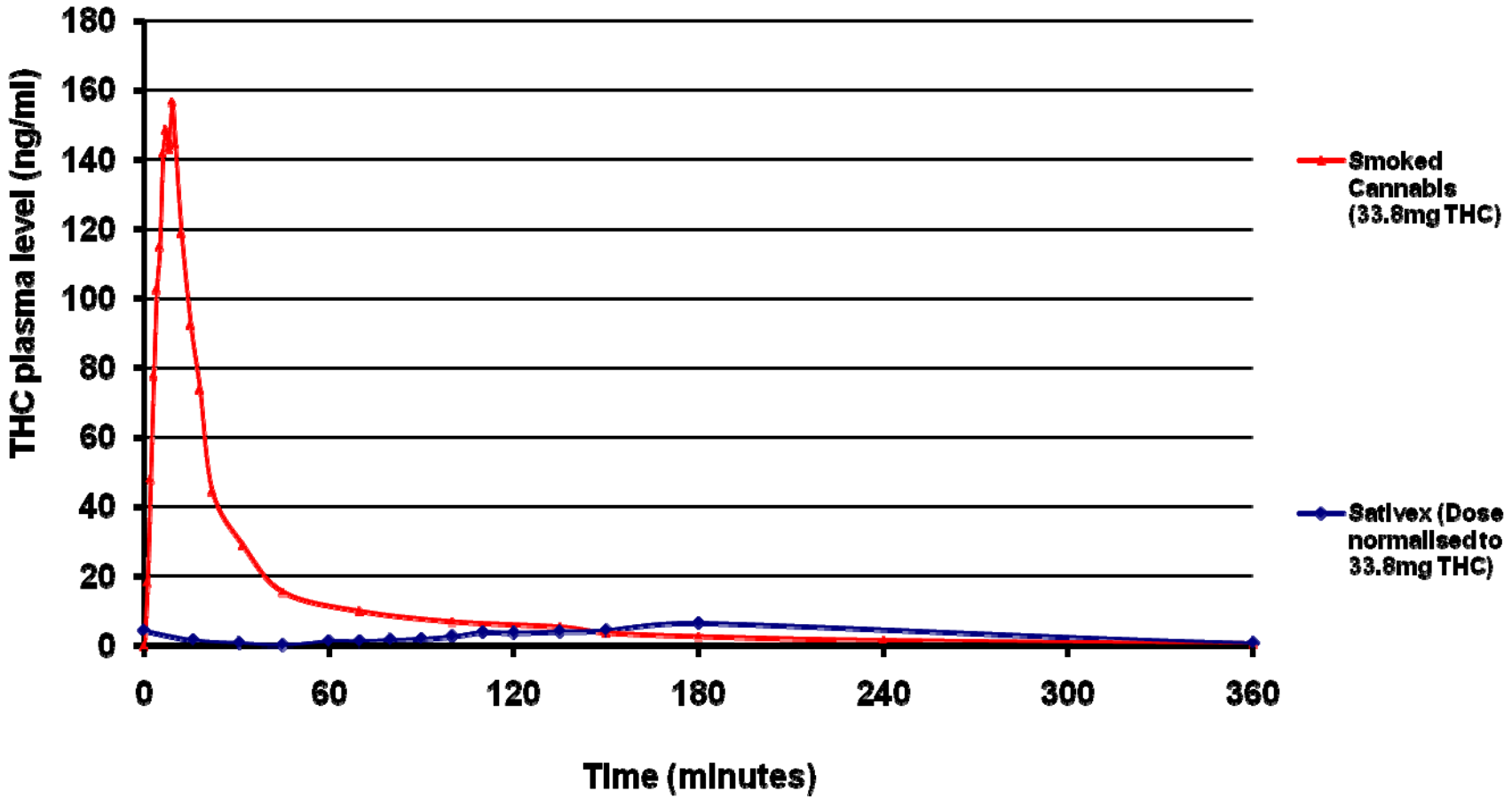
- Significant difference in availability between patients; need to be able to adjust individual dose
- Poorly soluble in water (unlike opiates)
- **Oral route**: poor bioavailability; psychoactive metabolite produced; prolonged (2-4 hours) onset of action so can't titrate
- **Inhaled/smoked route** makes THC levels rise too much/too soon, produces psychoactivity and increases drug abuse liability

Cannabinoid Therapeutic Window – Approaches?

- Cannabinoid ratios (CBD/THC) widen window
  - CBD counters some of the side effects, including intoxication
  - CBD:THC ratio has a unique therapeutic profile

- Route and method of delivery
  - Oromucosal route far less variable than Oral (GI)
  - Oromucosal absorption decreases production of psychoactive metabolite by liver
  - Intermediate onset of action allows patients to adjust and predictably individualize their dose
  - Rate of absorption is controlled: not too much THC too soon

Dose-normalised comparison of THC Levels from Smoked Cannabis (33.8mg THC) with nabiximols (Sativex) (12.5 sprays containing 33.8mg THC)



Products of the future

- Preparations of different cannabinoids (both synthetic and botanically-derived) and cannabinoid ratios, e.g., CBG, CBN, THCV, etc.
- Targeting CB_2 and other receptors, not just CB_1
- Modulating the endocannabinoid receptor system

It Takes Time!

- Improved technology and discovery of endocannabinoid receptor system means that we are only at the early stages of developing modern medications, i.e., numerous preclinical studies, gradually moving into clinical trials, etc.
- At some point soon, will be same distinction as there is with smoked opium (recreational use only) and modern opiate medications

One possible product

- Nabiximols (Sativex®) contains a defined (1:1) ratio of THC and CBD, as well as other minor cannabinoids, terpenes, etc.
- Finished pharmaceutical product derived from extracts of two unique strains of the cannabis plant
  - One strain is predominantly THC
  - Other strain predominantly CBD (cannabidiol), a non-psychoactive cannabinoid
  - Also contains other plant components, such as terpenes, flavonoids, etc.
- Novel delivery system—oromucosal spray
  - Intermediate onset of action, 15-40 minutes
  - Allows patients to individualize their dose
  - Each spray provides 100 mcl. of product, comprising 2.7mg. THC and 2.5mg. CBD


IVEX®
Oromucosal Spray
Cannabis sativa L. extracts
corresponding to 27mg/ml THC
and 25mg/ml CBD
5.5ml
GW
pharmaceuticals
EXP:
BN:

Questions?