# Cannabinoids and pain relief

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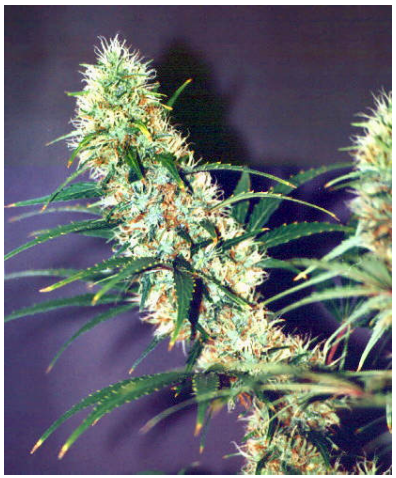
# Cannabis and cannabinoids

- Cannabis (plant) contains many cannabinoids and other active chemicals



Cannabis sativa

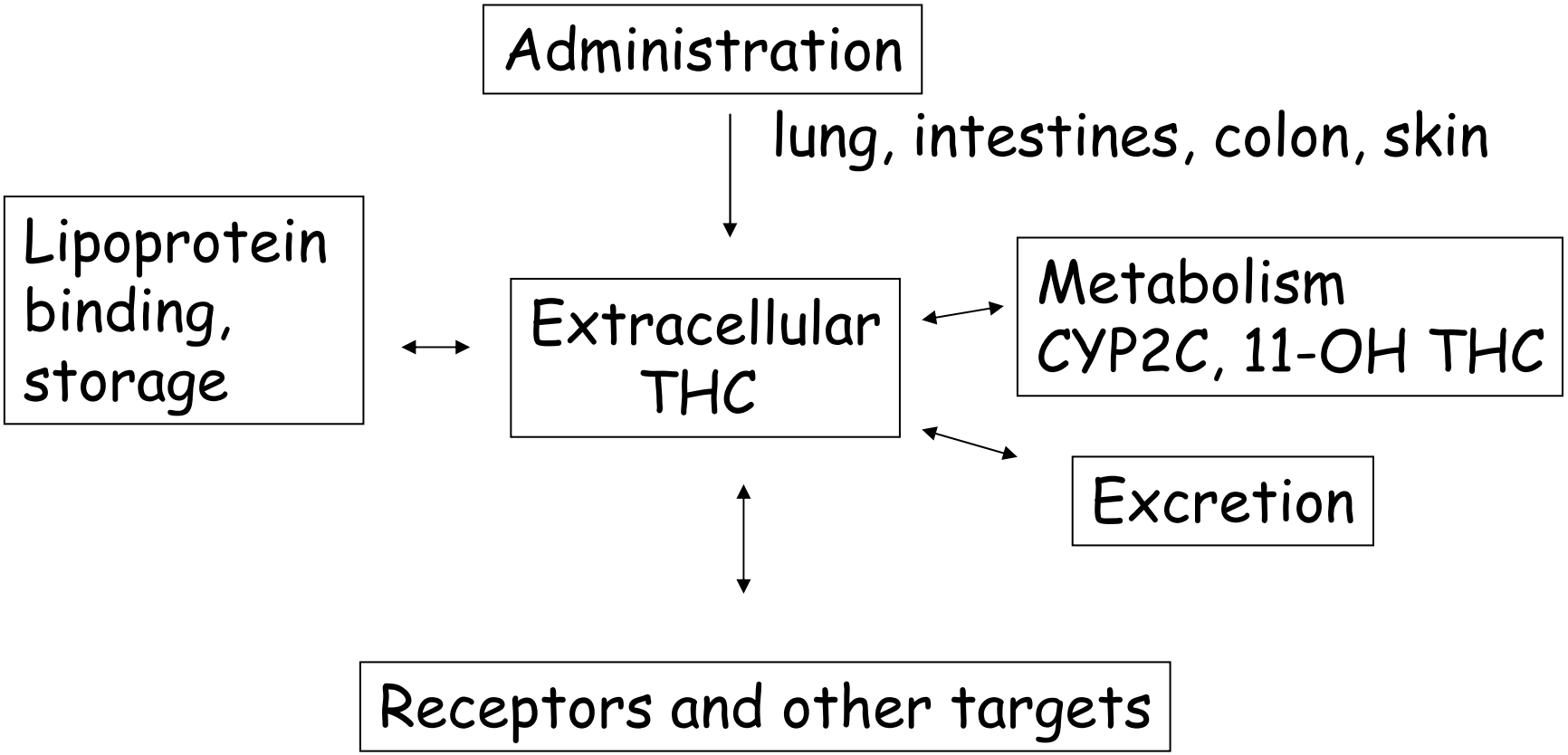
# Cannabinoids

Classification based on derivation:

- Phytocannabinoids (plant derived) e.g. tetrahydrocannabinol* (THC)
- Endocannabinoids (endogenous e.g. anandamide, 2-AG [arachydonylglycerol], PEA [palmitoylethanolamide])
- Synthetic derivatives: classical e.g. nabilone*; non-classical e.g. levonantradol

*licensed for clinical use

# Pharmacokinetics of THC



# How do cannabinoid receptors work?

**CB1 and CB2 receptors** are coupled through $G_i$ proteins to

- Inhibit adenylate cyclase
- Activate MAP kinase

**CB1 receptors** are coupled to

- P/Q type Ca channels (-)
- A-type K+$K_{ir}$ channels (+)

**The effects are to:**

- hyperpolarise nerve cells
- prevent release of neurotransmitters

Progress in Neurobiology 1999

# Where are the cannabinoid receptors?

CP 55,940 (active at cannabinoid receptors) attaches to cannabinoid receptors in the

a. Basal ganglia
b. Cerebellum
c. Hippocampus
d. Cerebral cortex

CB2 receptors are present in spleen

(Herkenham and Hohmann, 2002)

*Low toxicity of cannabis may relate to lack of receptors in brain stem

# Activity of cannabinoids

## General

- Antiemetic
- Regulation of immune and inflammatory processes
- Cardiovascular
- Antinociception
- other e.g. IOP

## Psychological

- Mood
- Cognition
- Memory

## Behavioural

- Hypothermia (animals)
- Movement disorders

# Potential drug interactions - depending on metabolic or receptor activity

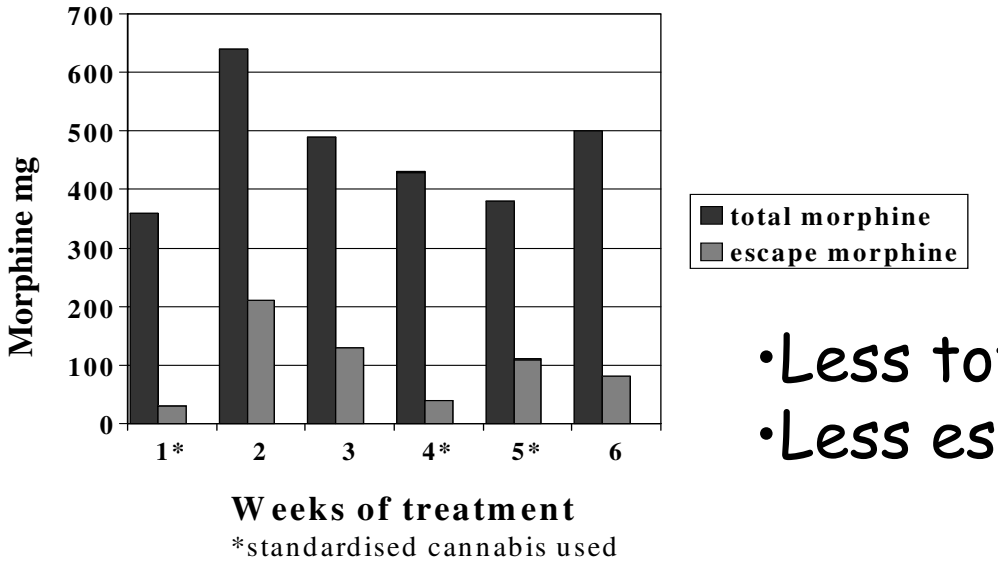
- Liver CYP450 enzyme system
  - cannabis smokers
- Central nervous system - sedation
  - alcohol, benzodiazepines
- Opioids
  - synergism
- Cardiovascular effects
  - sympathomimetics
  - anticholinergics

# Routes of administration for cannabinoids

- Oral - Marinol (THC), Cannador (Cannabis)
- Inhalational - aerosol, Thorax 1976
- Rectal - J Pharm Sci 1991, Marihuana & Medicine 1999
- Intramuscular - levonantradol, J Clin Pharm 1977
- Intravenous - THC, Clin Pharm Ther 1977
- Sublingual - CBME, Anaesthesia 2004 onwards
- Dermal - Int J Pharm 1988
- Eye drops - J Pharm Sci 1983

# Cannabis in Familial Mediterranean Fever (FMF)

Randomised, double blind, placebo controlled trial using oral THC 5.75%; CBD 4.73%; Cannabinol 2.42%




- Less total morphine
- Less escape morphine

Holdcroft et al 1997

# FMF Study Results

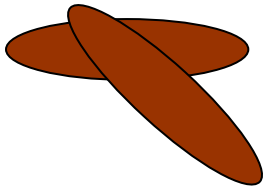
| | Active | Placebo |
|---|---|---|
| Urinary cannabinoid/ creatinine ratios $\mu g\ mmol^{-1}$ | 340 - 630 | 130 – 190* |
| Mean hourly VAS (0-10 cm pain intensity) | 4.8 – 6.2 | 5.5 – 6.1 |
| Escape morphine tablets (number) | 17 | 41* |

* P <0.001

# CANPOP multicentre clinical trial of cannabis in postoperative pain

Capsules -open label

PCA
Morphine
stopped

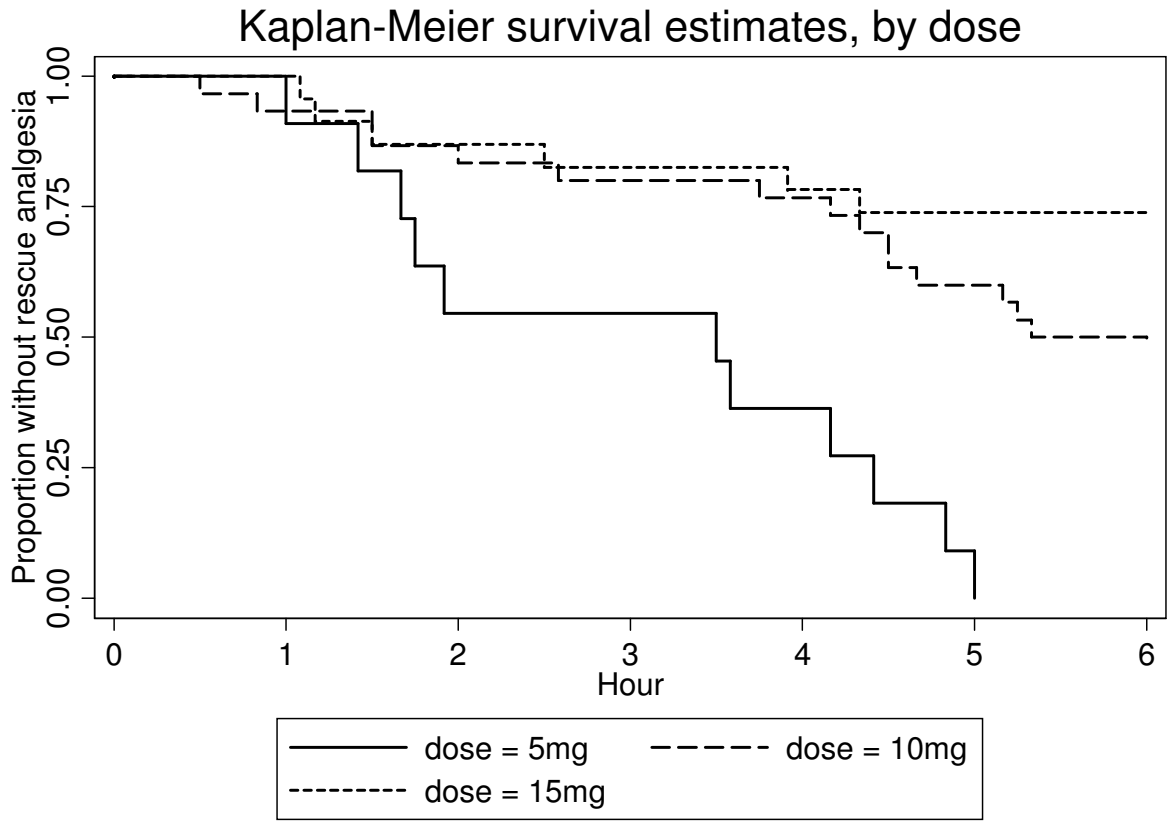


Over 6 hours:
Pain intensity
Pain relief
Side effects

Cannador = Cannabis extract
Capsules contain 2.5mgTHC + 1.25mgCBD
Doses: 5mg, 10mg and 15mg

Holdcroft et al 2006

# Time to rescue medication with 5mg, 10mg and 15mg Cannador

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# Results: adverse event severity

| *dose* | none | mild | moderate | severe [serious] | total |
|---|---|---|---|---|---|
| *5mg* | 10 | 1 | 0 | 0 | 11 |
| *10mg* | 24 | 5 | 0 | 1* | 30 |
| *15mg* | 5 | 13 | 3 | 2 [1] | 24 |
| total | 47 | 14 | 1 | 3 | 65 |

[* Protocol violation during recruitment] 5mg and 10mg vs 15mg P<0.002

# Adverse events for 15mg (10mg)

- Whole body 3 (0)
  - (pallor, pyrexia)
- Gastrointestinal 3 (0)
  - (dry mouth, vomit)
- Cardiovascular 4 (2)
  - (hypotension, hypoxia, cholinergic, tachycardia, pulmonary embolism)
- Central nervous system 9 (4)
  - (acute paranoia, cognitive function, light-headed, unpleasant mood, sensory disturbance, sleep disturbance, headache)

# CANPOP: other results

Trends with increasing dose for:

- More sedation (p = 0.03)
- More nausea (p = 0.06)

No changes with increasing dose for:

- Global evaluation (assessor/patient)
- Vomiting
- Mood
- Cardiovascular effects (±20% baseline)

# Summary:
# CANPOP results in postoperative pain:

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Cannador 5mg, 10mg, 15mg (THC content)

- 5mg had no demonstrable effect
- NNT 2 for 10mg, 1.3 for 15mg dose
- At 10mg and 15mg, dose-related pain relief achieved with >50% patients not requiring further analgesia over 6 hours
- Dose-related adverse effects increasing in severity

# Summary: cannabinoids

- Regular patient users of cannabis
  - MS, HIV, trauma, sickle cell
- Study drugs
  - plant derived, synthetic
- Licensed
  - Dronabinol/Marinol (THC)
  - Nabilone
  - In Canada: GW cannabis based medicinal extract CBME (THC/CBD) [Sativex] in MS

# Cannabis in pain management

'many normally law abiding citizens – probably many thousands in the developed world … use cannabis illegally for medical therapy'
British Medical Association 1997

# BBC Health Website 2007

- *"I've heard that cannabis can help multiple sclerosis (MS). I've had MS for five years now, and recently it's been getting a lot worse, with a lot of muscle spasm. Could cannabis help me, and if so, how do I get some?"*
- Dr (Named) First and foremost, I must point out that possession of cannabis is a **criminal offence**, although the police are more lenient with those possessing small amounts for their own personal medical use. There certainly have been claims that cannabis may have beneficial effects in a variety of medical conditions. It's used as a treatment for symptoms, not a cure.

# BBC Health Website 2007

- Dr (Named) continued

Herbal cannabis versus synthetic derivatives:

- The only legal option if you want to try cannabis for yourself… is to **talk to your doctor about drugs based on the main active component of cannabis**.
- These contain a synthetic version of THC, and are in tablet form, so you don't have to smoke them. The advantage is that it's legal, easy to take, and with a guaranteed dose. Some people who've tried it say that **it's not as effective as smoking herbal cannabis**, but many have found it has helped to some degree, although **side effects** may still be a problem.

# Cannabis in pain management

- What can we learn from patient experience?
- Who are these people?
- Do they use cannabis for recreation?
- How do they administer cannabis e.g. is it smoked, cooked or drink?
- What hazards do they face?

# Methods of use

- Oral
  - Tea
  - Brownie
- Vapourization
- Smoking

# Multiple sclerosis

The perceived effects of smoked cannabis on patients with multiple sclerosis. Eur Neurol 1997;38:44

Questionnaire (68Q, anonymous, 57% response rate)

Reason stated for use of cannabis:

- 103 (92%) to reduce MS symptoms, >50% disabled
    - 97% Spasticity
    - 95% Pain
    - 91% Tremor
- 43 (38%) to reduce MS episodes

# Multiple sclerosis

Reason stated for use of cannabis:

- 80 (71%) for relaxation
- 50 (45%) to relieve anxiety
- 47 (42%) to relieve depression
- 26 (23%) to obtain energy
- 24 (21%) to obtain a 'high'

# Multiple sclerosis

Patterns of use

- Duration 6 years (<1 – 28)
- Average number of times used per day = 3 usually in the evening
    - 58% Evening
    - 38% Before going to sleep

# Multiple sclerosis

Differences in cannabis use:

- Males ($P<0.05$),USA ($P<0.05$) subjects had smoked for a longer duration and more times per day than females or UK groups
- More USA subjects smoked as required at regular intervals ($P<0.05$)
- CBME now licensed in

  Canada for MS symptoms

# Multiple sclerosis - Canadian studies

- A study in Alberta with a 60% response rate found 16% of MS patients had used cannabis therapeutically
- 93% response rate found 34 (15%) MS patients has used cannabis (Neurology 2004)
    - 65% used cannabis for pain/sleep/spasms
    - 56% used cannabis for recreation
    - 71% were tobacco smokers
    - 85% used cannabis once at night
    - 35% used cannabis orally

# HIV

- Previous small studies in Honolulu, Alabama, California, Sydney
  (32-37% prevalence)

# Human Immunodeficiency Virus

- Cannabis use in HIV for pain and other medical symptoms at St Stephen's Centre, Chelsea & Westminster Hospital
  (J Pain & Symptom Management 2005)
- Questionnaire study (piloted)
- Ethics approval (anonymous)
- Consecutive patients at walk in clinic
- Refusals recorded

# HIV – questionnaire results

- 523 completed study (93% response rate)
- 27% used cannabis to treat HIV symptoms
- Longer duration of HIV and more disabled people were cannabis users ($p<0.01$)
- 75% were current users at least once a week; 64% after 6.0pm

Routes used:

- 71% smoked cannabis
- 27% smoke, ate and drank cannabis
- 2% only ingested cannabis

# HIV – questionnaire results

## Reasons for use:

- 85% to relax
- 66% to reduce anxiety
- 54% to relieve HIV symptoms
- 52% to relieve depression
- 43% for a 'high'

## Symptoms that had improved:

- 79% appetite
- 63% pain in muscles, nerves (neuropathy), sensory abnormalities
- 56% nausea
- 98% anxiety and depression

# HIV – questionnaire results

Reported side effects:

- 13% Memory loss
- 2% Nausea
- 2% Anxiety
- 2% Tiredness
- 2% Diarrhoea

# Issues raised

- Large numbers using cannabis as therapy
- Use of a non-medical supply exposes patients to non-standard products (toxins, dose etc)
- Unable to divulge use to
  medical team potential
  drug interactions
- Only medical use documented
  not purely recreational use
- Pattern of on going regular medication for which subjects derive benefit

# Sickle cell disease

- Cannabis use in sickle cell disease: a questionnaire study

  Br J Haematology 2005

  Howard, Anie, Holdcroft, Korn, Davies
- Central Middlesex Hospital

# Sickle cell disease

Aimed to record:

- Adult patient experiences with cannabis
- Extent of use for symptom relief
- Side effects

Methods:

- Structured anonymous questionnaire
- In HbSS, HbSC, HbSßthalassaemia
- 86 patients recruited (mean age 30y)

# Sickle cell disease

- 36% used cannabis to relieve symptoms
- Route:
    - 94% smoked cannabis
    - 10% used oral route
- Frequency of use:
    - 57% used cannabis in the evening
    - 13% Daily (range 2-6 times)
    - 32% Weekly
    - 13% Monthly
    - 42% Occasional

# Sickle cell disease

Reasons for use:

- 52% to reduce pain
- 42% to reduce the amount of analgesics
- 29% to reduce chronic pain from SCD*
- 23% to reduce pain in acute exacerbations of SCD
- 10% to prevent pain from SCD
- 16% to get a 'high'
- 16% to reduce anxiety

* Includes avascular necrosis of head of femur (n = 4)

# Sickle cell disease results

Side effects/symptoms

- 42% sleepy
- 35% mood change (13% 'improved')
- 16% anxiety*
- 10% memory loss
- 6% dizziness

* Reported less anxiety with cannabis use in another part of the questionnaire

# Sickle cell disease results

Future studies

- 50/86 (58%) were keen to contribute to studies on cannabis for pain relief in SCD of whom 24 (48%) were cannabis users
- 36 (42%) were concerned about dependency of whom 9 (25%) were cannabis users

# Cannabis use in HIV & SCD

## Study conclusions:

- Demographics (age, gender) similar to disease population
- High frequency of cannabis use for acute and chronic pain exposes patients to
    - Toxins
    - Drug interactions
- Reports of severe pain & disability
- Side effects identified but they do not deter from use
- Patients willing to enter clinical trials of cannabinoid medication

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