Medical Cannabis Conundrums

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Context

- By-product of policy debate about cannabis use
  - no "medical marijuana" debate if cannabis were legal
- Polarisation of policy debate:
  - Reformers support medical uses of marijuana
  - Prohibitionists oppose any medical use
  - Difficulties in finding a policy compromise
- Literature dominated by partisans
  - Opponents of any medical cannabinoid use
  - Proponents of "medical marijuana" as a panacea

Key Questions

- Do cannabinoids have medical uses?
- Are pharmaceutical cannabinoids the solution?
- Should cannabis be smoked for medical purposes?
- If so, how can this be done given:
  - the prohibition on recreational use
  - pharmaceutical regulatory requirements
  - issues of equity in funding medical treatments?

Defining some key terms

- Cannabis: any product of *cannabis sativa*
    - Marijuana: flowering tops
    - Hash: compressed resin
    - Cannabis extracts e.g. Sativex
- Cannabinoids for potential medical use:
  - Cannabis extracts e.g. Sativex (THC:CBD)
  - Drugs derived from cannabis plants (THC/CBD)
  - Synthetic drugs that act on cannabinoid receptors
    - agonists or antagonists

Medical Uses of Cannabinoids

- **Major uses for symptom relief**
  - Usually as an adjunctive or second line treatment
- **Major putative medical benefits :**
  - controlling nausea and vomiting *
  - Stimulating appetite *
  - reducing muscle spasticity & pain in MS *
  - reducing intraocular pressure in glaucoma
  - chronic pain

Nausea and Vomiting

- **Older indication with evidence of efficacy:**
  - RCTs conducted in 1970s and 1980s
- **THC had anti-emetic effects**
  - compared to prochlorperazine
  - anti-emetic effects of THC modest (30% control of emesis)
  - newer drugs much more effective (90% control of emesis)
    - with fewer side-effects including psychoactive ones
- **Smoked cannabis**
  - much weaker evidence
  - very limited use in intractable cases

Wasting Syndrome & Anorexia

- **Cannabis in AIDS-related wasting**
  - anecdotal evidence of benefit from smoking cannabis
  - AIDS advocacy groups campaigned for right to use
- **Dronabinol approved by FDA for this use 1985**
  - but limited use: difficulties titrating dose & side effects
  - Cochrane review concluded evidence weak
- **Main role as an adjunctive treatment**
  - Little used now because of advent of HART
  - Few HIV infected persons progress to clinical AIDS

Neurological Disorders

- Treat muscle spasticity & neuropathic pain in MS
- Sativex: a medical extract from cloned cannabis plants
  - One with high THC and one with high CBD
  - Combined to produce a THC:CBD ratio of 1:1
  - Delivered by oromucosal spray under the tongue
- Rationale:
  - Quality controlled defined dose of THC:CBD
  - CBD to moderate psychoactive effects of THC
  - Avoids smoking as a route of administration
  - Method of production patentable

Meta-analysis of Trials in Neuropathic Pain

- Iskedjian et al (2007) funded by GW
  - 6 studies with 298 patients
- Significant reduction in pain for all cannabinoids
  - 1.5 points on 10 point scale vs 0.8 for placebo
- Clinical significance?
  - Usually 2 point reduction required for "significance"
  - Little evidence of objective motor improvement

Acute Risks
(e.g. if used as an anti-emetic)

- Major risk: impaired psychomotor performance
  - Increased risk if patients drive: advise them not to drive
- "Within limits tolerated for medications" (IOM, 1999) when used for:
  - for short periods of time
  - in the absence of major contraindications
- Low rate of adverse events in Sativex trials
  - Dizziness the most common
  - Fewer adverse psychoactive effects
  - Low rating of "high"

Risks of Chronic Cannabis Use?

- Know most about adverse effects of recreational use:
  - Smoked cannabis in adolescents and young adults
- Uncertain how relevant these risks to medical use
  - In middle-aged and older adults with chronic illnesses
- Major Health Risks of possible relevance:
  - Dependence?
  - Myocardial infarction in high risk adults, if smoked?
  - Chronic bronchitis & possible malignancy, if smoked?

Are Pharmaceutical Cannabinoids the Answer?

- **THC registered as Dronabinol or Marinol**
  - Required public investment by NIH
  - THC is not patentable so orphan drug
- **But not widely used**
  - Oral route not well suited to THC
  - Difficult to titrate dose
  - High rates of adverse psychoactive effects
- **Sativex the current best hope**
  - Registered for MS in Canada, UK and parts of Europe
  - Will it be more acceptable than dronabinol?

Should we allow cannabis to be smoked for medical purposes?

- Why may we want to do so?
  - If Sativex is not used by patients
- Decriminalize medical use of marijuana
  - for specified medical indications
- Challenges:
  - Enforcement issues for police
  - Where do patients obtain their cannabis?
  - Equity issues raised by special access schemes

US Medical Marijuana Initiatives

- Citizen initiated referendum to allow medical marijuana
  - California 1996; 9 other US states since then
- In CA illicitly grown cannabis supplied via "compassion' clubs" to patients
  - with a recommendation from a medical practitioner
  - that patient has a condition that "may benefit from" cannabis
- Problems:
  - looseness of criteria: de facto legalisation in CA
  - Conflict between Federal and State laws
  - Continued uncertainty for patients and prescribers

Who Uses Medical Marijuana in California?

- Medical cannabis patients in SFO Bay Area 2001-2007
  - O' Connell and Bou-Matar (2007) N = 4117
- Characteristics:
  - 77% male; average age: 32 years
  - 89% had used cannabis before 19
  - 90% daily smokers of 1/8 to ¼ oz/week
  - Indications?
    - Given age unlikely to be AIDS, cancer or neurological diseases
    - Harm reduction for alcohol and other drug use disorders?
- A de facto marijuana maintenance program?

Canada's Medical Cannabis Program

- Since 1999 patients allowed
  - to possess and grow cannabis for their own use
  - Carers can do so if patients unable to do so
- Problems:
  - Reluctance of physicians to prescribe
  - Patient complaints about cannabis quality & cost
  - Low uptake and C$30M for 1900 patients since 1999
  - Equity of access to pharmaceuticals
    - Unapproved drug of uncertain safety and efficacy
    - When drugs of known efficacy are not subsidised

Medical Cannabis in the Netherlands

- Legal supply of medical cannabis by government
  - On prescription and dispensed by pharmacists
- Interesting policy setting
  - Cannabis use decriminalized since early 1970s
  - De facto retail cannabis market in coffee shops
- How much patient interest is there in medical use of cannabis if recreational use is effectively legal?

Medical Use in the Netherlands

- Survey of Dutch 5,540 medical cannabis patients 2003-2010
  - Hazekamp and Heerdink (2013)
- Incidence:
  - 6 per 100,000 for 2003-2004
  - 2 per 100,000 for 2005-2010
- Prevalence:
  - 5-8 vs 100 per 100,000 in some states in USA
- Indications (based on co-prescribed medications):
  - Pain (54%)
  - Cancer (3%)
  - HIV (1%)

Medical Cannabis Conundrums 1

- If cannabis is illegal it can only be prescribed
  - if approved by the regulatory system and
  - a company is prepared to supply it
- Smoked cannabis:
  - Unlikely to be approved for medical use
  - No financial incentive for companies to register
- So governments have created special access schemes
  - Ignored regulatory requirements & subsidized supply
  - Creating a worrisome precedent and
  - Raising equity issues

Medical Cannabis Conundrums 2

- Disincentives for pharma to develop new cannabinoids:
  - Patentability, profitability and regulatory burdens
- Approved medicinal cannabinoids not very popular
  - Dronabinol neither widely used nor profitable
- Sativex the current best hope:
  - But small market and modest efficacy to date
  - Will it prove acceptable
    - to patients and "medical marijuana" advocates?

Medical Cannabis Conundrums 3

- If medical cannabis use is legally allowed
  - Medical users need not fear prosecution
  - Reluctance of physicians to prescribe
  - But legal supply remains a problem
    - Unless Governments allow cultivation or supply it
  - If governments provide, an expensive program
  - Equity issues in providing unapproved drug