A Framework for Designing Medicinal Cannabis Clinical Trials in Palliative Care: Opportunities and Challenges

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Abstract

In recent years, global public advocacy has called for greater access to medicinal cannabis, especially for palliative care patients. However, health care practitioners are reluctant to use medicinal cannabis due to their lack of knowledge and inconclusive evidence. To address this, Australia is promoting clinical research on cannabis to expand the evidence-base for its legitimate use as a medicine. However, the complexity of undertaking medicinal cannabis clinical studies, especially involving palliative care populations, requires careful consideration of various legal, social, ethical and product/supply factors.

This presentation will discuss a framework which outlines the key challenges that need to be considered when designing and conducting high quality, yet safe and feasible clinical trials using medicinal cannabis, particularly in reference to symptom management in palliative care. Challenges for the drug's future translation into clinical practice are also discussed.

Background

Cannabis (*Cannabis sativa* L. Cannabaceae) is one of the oldest plants cultivated by man for fibres since 4000 BC. Its use as a medicine, mainly the cannabis seed, dates back to around 2700 BC in China, and its psychoactivity known in India around 1000 BC.

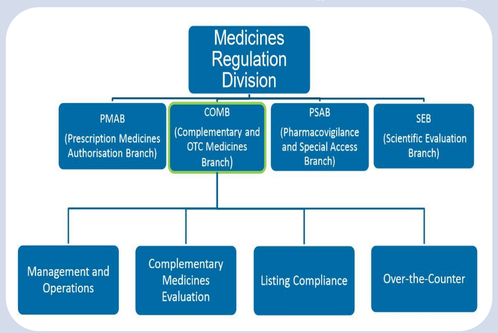
Thus, much of society has seen cannabis as an illegal drug, rather than a therapeutic agent. Recently, the socio-political environment has shifted toward potential for legitimate medical use, especially in palliative care.

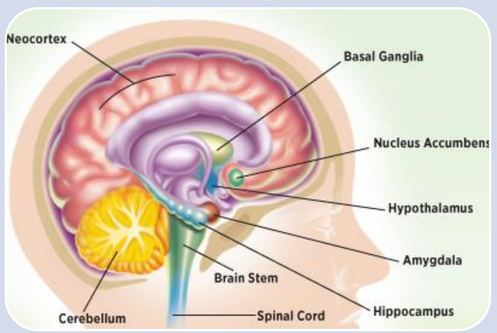
However, clinical trials in people with cancer have shown inconsistent results for its benefits and role for widespread use as a therapeutic agent for symptom management.

The limitations of previous studies include:

- Sample size and duration of study
- Delayed response of oral absorption
- Lack of pharmacokinetic studies
- THC-only drugs having a narrow therapeutic index that limited the delivery of effective doses
- Difficult to compare products/dosing/timing
- Variability in assessments

Figure 1: Key challenges in planning a botanical medicinal cannabis trial.





Legislation

- Scheduling of product (S8 - drug of addiction for cannabinoid content over 2%)
- Permits (export, import, transport)
- Plant material microbe check (Australian Quarantine & Inspection (AQIS))
- Prescriber and pharmacy authorisations

Biological

- Pharmacodynamic (symptoms, quality of life; qualitative, longer term benefits)
- Pharmacokinetic (time points of blood sampling correlated to symptom relief and/or toxicity; metabolites)
- Product characteristics (single and combinations of compounds; extracts versus whole plant; stability; ease of administration)

Human Ethics

- Safety of participants (safety monitoring and 24-hr care)
- Equipoise (hypothesis, eligibility, treatment arms)
- Current alternative treatment options (and their limitations)
- Driving (offence to drive with detectable cannabinoids)
- Staff exposure (especially for inhaled cannabis in the hospital setting)

Product

- Choice of product variety
- Standardisation of cannabinoid content (to a particular compound or quality profile of plant material: certificate of analysis)
- Dosage (fixed amount of cannabis per day or self-titration)
- Mode of administration (vaporised, smoked, tablet, tincture, oil, spray, tea)

Pharmaceutical

- Packaging of dosage forms (protection from moisture and light)
- Pharmacy dispensing (handling authority, procedures to follow local scheduling of product)
- Storage and security of product (fridge bolted down or in safe; certified courier for transporting products)

Operationalisation

- Choice of location of trial (inpatient or community)
- Personnel (availability of clinical, pharmacy and analytical staff)
- Travel (sites, conferences)
- Training (GCP, protocol)
- Equipment (hospital, pathology and laboratory)
- Consumables (sampling, general ward items)

Challenges

The key challenges in planning a trial of a medicinal cannabis product involve (Figure 1):

1. *Knowledge of current, local (in this case Australian) legislation of cannabis
2. *Biological plausibility of cannabinoid type(s) and impact on target symptoms
3. Maintaining Human Research Ethics requirements
4. *Product considerations
5. *Pharmaceutical processes
6. Trial operationalisation

**Many of these challenges will need to be considered when implementing medicinal cannabis use in clinical practice*.

Opportunities

- Medicinal cannabis may provide relief for a variety of symptoms.
- Palliative population welcomes the opportunity and benefits from contributing to well-designed studies and trials.
- Specific funding available for cannabis research.
- Local (and international) industry is expanding and wanting to collaborate with research.
- Specialised cannabis centres have been set up
- Working with stakeholders including local and international regulatory and legal authorities and organisations, health care personnel and facilities, industry and various researchers.
- Future PBS inclusion

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Selected References

Australian Government Department of Health Therapeutics Goods Administration. Access to medicinal cannabis products. https://www.tga.gov.au/access-medicinal-cannabis-products
Berry EM, Mechoulam R. Tetrahydrocannabinol and endocannabinoids in feeding and appetite. Pharmacology & Therapeutics 2002;95(2):185-90.
Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. Clinical Pharmacokinetics 2003;42(4):327-60.
Hazekamp A, Ware MA, Muller-Vahl KR, Abrams D, Grotenhermen F. The medicinal use of cannabis and cannabinoids—an international cross-sectional survey on administration forms. Journal of Psychoactive Drugs. 2013 Jul 1;45(3):199-210.
International Association for Cannabinoid Medicines. Clinical studies and case reports. http://www.cannabis-med.org/studies/study.php.
McPartland JM, Russo EB. Cannabis and cannabis extracts: greater than the sum of their parts?. Journal of Cannabis Therapeutics. 2001; 1(3-4):103-32.
Zuardi AW. History of cannabis as a medicine: a review. Revista Brasileira de Psiquiatría 2006; 28(2):153-57.