Medicinal cannabinoids – where does it fit in Palliative Care?

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Medicinal cannabis

• Substantial public interest
• Legalised by the Qld Government
• Guidance documents for use in epilepsy, CINV, multiple sclerosis, chronic pain, palliative care published December 2017
• Clinical Guidance for the use of medicinal cannabis products in Queensland (March 2018)
Medicinal cannabis

- Pharmaceutical grade medicinal cannabinoids

- Cannabis contains almost 500 bioactive compounds, including over 70 different cannabinoids

- Predominant cannabinoids: delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD).
Medicinal cannabis

• THC – psychoactive

• Potential benefits - analgesia, anti-nausea, and muscle relaxation

• Potential side effects - intoxication, psychosis, anxiety and sedation.
Medicinal cannabis

• CBD is not intoxicating

• Potential benefits - anxiolytic, antipsychotic, anti-inflammatory, anti-oxidative, anti-convulsant and neuroprotective effects

• CBD is also considered to mediate many of the adverse psychotropic effects of THC
What is the evidence of benefit?
Medicinal cannabis - evidence

- UK commissioned review (Barnes, 2016)
- good evidence for use in chronic pain, spasticity, CINV, anxiety
- moderate evidence in chemo induced anorexia, sleep disorders, PTSD, fibromyalgia, Parkinson’s disease symptoms
- “much further work needed with regard to best formulation, and best ratio for different conditions”
Medicinal cannabis - evidence

• USA National Academy of Sciences (2017)

• substantial evidence for benefit in chronic pain, CINV, spasticity in MS

• moderate evidence in sleep disorders
Medicinal cannabis - evidence

• systematic review (Whiting et al, 2015):
  • moderate quality evidence for chronic pain and spasticity
  • low quality evidence for chemotherapy induced nausea and vomiting (CINV), sleep problems, HIV related anorexia, and Tourette syndrome
• adverse events - odds ratio in the cannabinoid arm was 3.03 (95%CI: 2.42-3.80)
• most common adverse effects - disorientation, confusion, dizziness, euphoria, drowsiness, psychiatric disorders and dry mouth.
Why do people believe it works?

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812      MAY 25, 2017      VOL. 376      NO. 21

Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome

Orrin Devinsky, M.D., J. Helen Cross, Ph.D., F.R.C.P.C.H., Linda Laux, M.D., Eric Marsh, M.D., Ian Miller, M.D., Rima Nabbout, M.D., Ingrid E. Scheffer, M.B., B.S., Ph.D., Elizabeth A. Thiele, M.D., Ph.D., and Stephen Wright, M.D., for the Cannabidiol in Dravet Syndrome Study Group*
Medicinal cannabis trials registered with ANZCTR

• Early phase clinical trial to assess dose-response, feasibility and safety of cannabinoids in patients undergoing ileostomy closure.

• Randomised, Double Blind, Placebo-Controlled, Crossover Trial of THC and CBD for Tourette’s Syndrome

• The efficacy of sublingual cannabinoid based medicine extract compared with placebo for Insomnia.

• A Phase 2 Double-Blind RCT assessing the efficacy of Medicinal Cannabis in patients with recurrent Glioblastoma Multiforme (GBM).

• A Phase II, Randomized, Placebo-Controlled, Double Blind, Trial of Safety, Tolerability and Efficacy Study of Topical AKP-11 in Arthritis.

• The cannabidiol youth anxiety pilot study (CAPS): a 12-week open-label pilot study of the safety, tolerability and efficacy of cannabidiol for anxiety disorders.
Medicinal cannabis trials registered with ANZCTR

- A Phase II, safety, tolerability and efficacy study of topical AKP-11 administration to participants with atopic dermatitis*.

- CannabisCINV: Pilot and definitive randomised double-blind placebo-controlled trials evaluating an oral cannabinoid-rich THC/CBD cannabis extract for secondary prevention of chemotherapy-induced nausea and vomiting*

- Cannabidiol (CBD) for Cannabis and Mood Disorders in Adolescence (CCAMDA)

- The effects of medicinal cannabinoids on driving in healthy adults with prior cannabis experience

- Sativex Oromucosal Spray to reduce pain in patients with chronic ischaemic chest pain
Medicinal cannabis in palliative care?
Johnson 2009

- RCT in cancer pain
- 2 weeks duration
- THC vs THC/CBD vs placebo
- oromucosal spray
- average pain ≥4, on opioids
- each pump delivered 2.7mg THC +/- 2.5mg CBD,
- self titrated
- previous cannabis use 10-12%
Johnson 2009

- 177 randomised,
- median dose OME 80-120mg/day
- mean sprays/day: THC 8.47, THC/CBD 9.26, placebo 10.88
- mean reduction in pain score (11-point NRS): THC/CBD -1.37 (p=0.014), THC -1.01 (NS), placebo - 0.69
- no change in baseline or breakthrough medication
- QOL – no difference (although increased nausea/vomiting in THC/CBD)
Fallon 2017

- Study 1 - RCT, blinded
- cancer pain
- THC/CBD vs Placebo
- 2 week titration then 3 week maintenance

- Study 2 - enriched design
- THC/CBD titration for 10 days, then 4 days therapy
- If 15% improvement on NRS progressed to Part B
- Part B: RCT – THC/CBD vs placebo for 3 weeks

- Primary outcome:
  - Study 1 - % improvement in average NRS
  - Study 2 – mean change in average NRS
Fallon 2017

- study 1 - 399 enrolled
- study 2 - 406 enrolled
- average NRS 5.6-5.8
- breakthrough daily use – 57-71%
- mean OME/day 199-218mg/day
- Study 1: 7.4 vs 6.3 sprays per day
- Study 2: 6.5 vs 6.3 sprays per day

Results
- study 1 - no difference (7.2% vs 9.5%)
- study 2 - no difference (+ 0.5 in both groups)

- SGIC/PGIC improved in THC/CBD group (Study 1 only)
Portenoy 2012

- patients with advanced cancer
- poor response to prior opioids
- Nabiximols (Sativex) spray at low, medium or high dose
- randomised, double-blind, placebo-controlled, graded dose study
- primary outcome measure (30% responder rate) = NS
- secondary analyses, benefit for Nabiximol in certain subsets
Unreliable analgesia
Cannabis spray – Phase II studies

![Graph showing percent change from baseline in NRS average pain score for different groups: Placebo, Nabiximols 4 Sprays (p=0.008), Nabiximols 10 Sprays (p=0.038), Nabiximols 16 Sprays (p=0.68).]
Unreliable analgesia
Cannabis spray
### Table 4. Treatment-emergent adverse events in ≥5% in study 1.

<table>
<thead>
<tr>
<th>Event, n (%)</th>
<th>Sativex (n = 199)</th>
<th>Placebo (n = 198)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All causality</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>136 (68.3)</td>
<td>127 (64.1)</td>
</tr>
<tr>
<td>Neoplasms progression</td>
<td>32 (16.1)</td>
<td>36 (18.2)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>24 (12.1)</td>
<td>8 (4.0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>19 (9.5)</td>
<td>16 (8.1)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>18 (9.0)</td>
<td>13 (6.6)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>16 (8.0)</td>
<td>9 (4.5)</td>
</tr>
<tr>
<td>Constipation</td>
<td>10 (5.0)</td>
<td>13 (6.6)</td>
</tr>
<tr>
<td><strong>Treatment-related</strong>b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>64 (32.2)</td>
<td>41 920.7</td>
</tr>
<tr>
<td>Somnolence</td>
<td>18 (9.0)</td>
<td>6 (3.0)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>15 (7.5)</td>
<td>6 (3.0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>10 (5.0)</td>
<td>8 (4.0)</td>
</tr>
</tbody>
</table>
### Safety (Fallon)

**Part B: Double-blind randomized treatment**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment 1</th>
<th>Treatment 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All causality</strong></td>
<td>103</td>
<td>103</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>74 (71.8)</td>
<td>64 (62.1)</td>
</tr>
<tr>
<td>Neoplasm progression</td>
<td>30 (29.1)</td>
<td>15 (14.6)</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>7 (6.8)</td>
<td>4 (3.9)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>6 (5.8)</td>
<td>7 (6.8)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>6 (5.8)</td>
<td>6 (5.8)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>6 (5.8)</td>
<td>3 (2.9)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>6 (5.8)</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td><strong>Treatment-related</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>16 (15.5)</td>
<td>12 (11.7)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>6 (5.8)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>
Why do people want it?
Reasons for use

Figure 3. Reasons for cannabis use among the survey respondents. The reasons for use were not mutually exclusive responses. Overall, the respondents used cannabis for physical symptoms (165 of 219 [75%]), for neuropsychiatric symptoms (139 of 219 [63%]), recreationally (76 of 219 [35%]), and to treat cancer (58 of 219 [26%]).
How do people want to take it?
Luckett 2016

• To explore the preferences, attitudes and beliefs of people with advanced cancer who self-identified as willing to consider participating in a clinical trial of medicinal cannabis for poor appetite and appetite-related symptoms.

• Electronic/Hard Copies, OPD palliative/cancer services – NSW and SA

• 13% prior use of medicinal cannabis (majority – smoked)
Table 2  Patient preferences for modes of delivery in a hypothetical clinical trial of medicinal cannabis for anorexia, appetite loss and taste change from advanced cancer (n = 204)

<table>
<thead>
<tr>
<th>Preferred mode</th>
<th>n †</th>
<th>% †</th>
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</thead>
<tbody>
<tr>
<td>Tablets or capsules</td>
<td>144</td>
<td>71</td>
</tr>
<tr>
<td>Mouth spray</td>
<td>84</td>
<td>42</td>
</tr>
<tr>
<td>Vaporiser</td>
<td>83</td>
<td>41</td>
</tr>
<tr>
<td>Eating</td>
<td>76</td>
<td>37</td>
</tr>
<tr>
<td>Drinking</td>
<td>68</td>
<td>33</td>
</tr>
<tr>
<td>Topical</td>
<td>53</td>
<td>26</td>
</tr>
<tr>
<td>Suppositories</td>
<td>16</td>
<td>8</td>
</tr>
</tbody>
</table>

†Participants could select >1 preference from the list given.
So, what do we know about Medicinal cannabis in palliative care?

- probable benefit in chronic pain but little benefit in cancer pain
- patients want it for symptom control (pain, nausea, appetite, stress, coping, mood) and to fight cancer
- oral route is preferred (tablets or capsules)
- unknowns: which cannabinoid, which combination, what dose, for how long for what indication?
Medicinal Cannabis – role in Palliative Care?

- Qld legislation
- Patient class prescriber
  - terminally ill persons being treated by a compliant palliative medicine specialist for symptoms associated with terminal illness
  - *terminally ill person* means a person who:
    (a) has a terminal illness; and
    (b) is, in the opinion of a compliant palliative medicine specialist treating the person, reasonably expected to die within 1 year as a result of the terminal illness

- Authorised prescriber
- Clinical trial
Welcome to Cannabis Access

This website will help you prescribe medicinal cannabis to your patients via the Special Access Scheme (SAS).

1. Register Online
   Register with CannabisAccess for restricted access to medicinal cannabis products available in Australia.

2. Complete e-Forms
   Browse products and apply for patient prescription approval:
   - **Part A:** Apply for Therapeutic Goods Administration (TGA) approval via the Special Access Scheme (SAS B).
   - **Part B:** Apply for state approval (NSW, SA, ACT, QLD, WA only).
   *Both part A and B can be done concurrently.

3. Wait Approval
   Wait up to 6 working days for TGA approval.
   Wait for state approval if required.

4. Order and Dispense
   Product can be ordered via CannabisAccess only once the TGA approval has been granted.
   If state approval applies, the product can only legally be dispensed once state approval is also granted.
**Tilray FS THC10:CBD10**
- **Supplier:** Tilray
- **Trade name / device name:** Tilray FS THC10:CBD10 (Previously TC100)
- **Dose Form:** Oil Solution
- **Recommended price per unit:** £6 price to pharmacy. Excludes shipping and GST.
- **Strength:** 10mg/mL + 10mg/mL
- **Package:** 25mL Vial
- **Lead Time:** 1 – 3 days

**Cannimed 10:10**
- **Supplier:** Health House International
- **Trade name / device name:** Cannimed 10:10
- **Dose Form:** Oil
- **Recommended price per unit:** £35 (Includes shipping fee)
- **Strength:** 10mg CBD 10mg THC per mL
- **Package:** 60mL Vial
- **Lead Time:** 24 hours

**Satipharm 50 mg**
- **Supplier:** Satipharm
- **Trade name / device name:** CBD Capsules 50 mg
- **Dose Form:** Capsule
- **Recommended price per unit:** To be confirmed
- **Strength:** 50mg / Capsule
- **Package:** 30 capsules per box
- **Lead Time:** 1–3 Days
**Tilray CBD10**
- **Supplier:** Tilray
- **Trade name / device name:** Tilray P CBD10 (previously CBD10)
- **Dose Form:** Oil Solution
- **Recommended price per unit:** $150 (price to pharmacy, excludes shipping and GST)
- **Strength:** 10 mg/mL
- **Package:** 25 mL Vial
- **Lead Time:** 1-3 days

**Cannimed 1:20**
- **Supplier:** Health House International
- **Trade name / device name:** Cannimed 1:20
- **Dose Form:** Oil
- **Recommended price per unit:** $350 (includes shipping fee)
- **Strength:** 1 mg THC, 20 mg CBD / mL
- **Package:** 60 mL Vial
- **Lead Time:** 24 hours

**GD Cann-C**
- **Supplier:** GD Pharma
- **Trade name / device name:** GD Cann-C
- **Dose Form:** Oil Solution
- **Recommended price per unit:** $270
- **Strength:** CBD 100 mg / mL
- **Package:** 10 mL Vial
- **Lead Time:** 1-3 days
Where does it fit?

- consumer driven
- non pharmaceutical companies
- little evidence of benefit
- few authorised prescribers to date
- ?future legalisation for recreational use
## Know your pot stocks

<table>
<thead>
<tr>
<th>Names</th>
<th>Code</th>
<th>2017 profit (Sm)</th>
<th>Market capitalisation ($)</th>
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</thead>
<tbody>
<tr>
<td>LIFESTOP HEALTH</td>
<td>LSH</td>
<td>N/A</td>
<td>$12,365,129</td>
</tr>
<tr>
<td>ATLAS PEARLS</td>
<td>ATP</td>
<td>0.9</td>
<td>$14,119,768</td>
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<tr>
<td>ESENSE-LAB</td>
<td>ESE</td>
<td>N/A</td>
<td>$18,140,524</td>
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<tr>
<td>CANNPAL ANIMAL THERAPEUTICS</td>
<td>CPI</td>
<td>N/A</td>
<td>$19,556,250</td>
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<tr>
<td>STEMCELL UNITED</td>
<td>SCU</td>
<td>-3.63</td>
<td>$19,958,193</td>
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<tr>
<td>CHAPMANS LIMITED</td>
<td>CHP</td>
<td>0.91</td>
<td>$20,800,000</td>
</tr>
<tr>
<td>BOD AUSTRALIA</td>
<td>BDA</td>
<td>-3.17</td>
<td>$30,537,440</td>
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<tr>
<td>EVE INVESTMENTS</td>
<td>EVE</td>
<td>-4.05</td>
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<td>ALGAETEC</td>
<td>AEB</td>
<td>-3.79</td>
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<td>RGI</td>
<td>-1.01</td>
<td>$53,623,361</td>
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<td>BOTANIX PHARMACEUTICALS</td>
<td>BOT</td>
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<td>$70,604,468</td>
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<td>HYDROPONICS COMPANY</td>
<td>THC</td>
<td>-0.21</td>
<td>$104,552,481</td>
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<td>ZELDA THERAPEUTICS</td>
<td>ZLD</td>
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<td>CRESO PHARMA</td>
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<td>-4.58</td>
<td>$110,600,599</td>
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<td>MMJ PHYTOTECH</td>
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<td>-12.73</td>
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<td>MGC PHARMACEUTICALS</td>
<td>MXC</td>
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<td>$115,155,846</td>
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<td>MEDLAB CLINICAL</td>
<td>MDC</td>
<td>-3.66</td>
<td>$184,075,325</td>
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<tr>
<td>CANN GROUP</td>
<td>CAN</td>
<td>-2.59</td>
<td>$453,526,551</td>
</tr>
</tbody>
</table>

*Source: Bloomberg*
Marijuana moguls optimistic about legalisation of recreational cannabis in Australia

Four Corners

By Sean Nicholls, Lisa McGregor and Stuart Washington
Barriers

- Funding
- Accessing product
- Regulatory hurdles
- Suppliers expertise and expectations
- Pharmacy requirements
- Participant issues
Future Research

- Pharmacogenomic studies that assess what genomic variations may help predict clinical outcomes
- Assessment of driving safety
- Pharmacodynamic/Pharmacokinetics