Use of cannabinoids in symptom management
Why cannabinoid therapeutics?

A need, evidence and a therapeutic product existed

Ministry of Health

- Developed therapeutic guidelines for cannabinoids (2007)

Cross-professional guideline review
Clinical leads of palliative care, GP, oncology, pain, along with Medsafe.

Liaise with pharmaceutical company (GW Pharma) review and stipulate requirements of quality safety & efficacy.

Engage and inform the Minister
Achieve seamless introduction through robust regulatory guidelines.
Why?

Further need exists, now with greater supporting evidence and therapeutic options

Palliative care setting (example)

Therapeutic option exist
Pharmaceutical quality (GMP) in various administration formats.

Clinical insight and clinical research
Trials (RCT) relevant to symptom management. Patient use worldwide.

A decade of use in New Zealand
Cannabis therapeutics now used in a community setting since 2008.
Despite its illegality, 42% of cannabis users reported using it medicinally in the last 12 months to treat pain, anxiety/nerves, depression, nausea.

Reference: Cannabis Use 2012/13: New Zealand Health Survey
Patients use

The problem with unregulated products – ‘illegal cannabis’

Cannabis, as a botanical substance, can vary greatly in cannabinoid content, from one plant to the next, and batch-to-batch.

This can lead to inconsistent and unpredictable effects.

Often illegal cannabis contains pesticides, heavy metals, and toxic moulds and fungus.
Patient use
New Zealand

104 applications to prescribe Sativex now approved (at January 2016)

Mainly prescribed off-label, that is for conditions other than MS.

Patient use
The Netherlands

The utilisation of medicinal-cannabis among the Dutch population who receive prescriptions for medicinal-cannabis suggest:

- Half of patients use another form of pain medication, 46% used psycholeptics, 44% used analgesics, 40% used anti-ulcer agents and 31% used NSAIDs.
- Medicinal-cannabis relieves patients’ pain, stimulates their appetite, reduces nausea and improves their sleep.
- On average, these patients use 0.7 grams of standardised cannabis flos per day, divided over multiple portions, for about 250 days in total.

Since 2003 the Dutch medicinal cannabis programme has delivered standardised cannabis flos, prescribed by doctors and dispensed by pharmacists.

Pharmacology
ligands and receptors

Endocannabinoid system
Essential role in homeostasis of bodily functions. Involved in regulation of appetite, sleep, pain, inflammation.

Cannabinoid receptors
CB1: CNS, heart, intestines, bladder. CB1 is one of the most prominent receptors in the brain.
CB2: immune system, spleen, tonsils

Exogenous ligands (phyto-cannabinoids). THC and CBD identified and isolated

<table>
<thead>
<tr>
<th>Cannabis plant - cannabinoids</th>
<th>Opium poppy – opium derivatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exogenous ligand – cannabinoids</td>
<td>Exogenous ligand – opioids</td>
</tr>
<tr>
<td>Cannabinoid G protein-coupled receptors</td>
<td>Opioid G protein-coupled receptors</td>
</tr>
</tbody>
</table>

Reference:
CB1 receptor
concentrated areas
nausea, appetite, pain, emotion

Medulla oblongata
nausea/vomiting centre
chemoreceptor trigger zone

Spinal cord
peripheral sensation
pain sensitivity

Cerebral cortex
Higher cognitive and emotional functions

Hypothalamus
appetite
Pharmacology

Phyto-cannabinoids

Endo-cannabinoids
Clinical trials
review of data

Between 2005 – 2015

- 69 studies
- 5860 patients

- Patient use surveys indicate pain as the main indication for medicinal cannabis use.

- The effects of cannabinoids on chronic pain is the most researched topic.

Chronic pain

Spasms (MS & epilepsy)
Palliative (sleep, appetite, relaxation)
Appetite, vomiting & nausea

Reference:
Palliative care is an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual.

In particular, palliative care:

• provides relief from pain and other distressing symptoms

• will enhance quality of life, and may also positively influence the course of illness

WHO Definition of Palliative Care: www.who.int/cancer/palliative/definition/en/
Palliative care setting

Compared to most other patients

- The doctor-patient relationship is more intensive and structured
- Prescribing is very well planned and monitored
- The risk of medicine diversion for misuse use may be less
- Adverse drug reactions are, possibly, more readily identified and resolved (and reported).

Types of palliative care-related prescriptions by category

- analgesics
- anti-emetics and anti-nauseants
- anti-epileptics
- anti-inflammatory & anti-rheumatics
- drugs for functional GI disorders
- laxatives
- psycholeptics
- stomatological preparations

Reverence: Palliative Care Services Australia 2014.
www.aihw.gov.au
In terms of palliative care, better understanding is needed of how cannabinoids might relieve nausea, or increase appetite, without side effects.

There is a lack of evidence about the efficacy and safety of cannabis-based therapies.

In particular, more is needed to know

• how to optimise the dose
• the best mode of administration
• the time that peak levels occur
• the length of time they are active
Clinical trials
wellbeing

The first of its kind in Australia, a double-blind randomised controlled trial (led by Professor Meera Agar, a NSW palliative care specialist) will explore whether vaporized medicinal cannabis flos can promote appetite and improve quality of life among cancer patients.

Vaporised cannabis flos
- Eliminates the respiratory risks of smoking
- Allows reliable dosage
- Is suitable for patients finding swallowing difficult.

Study protocol
- Delivers therapeutic concentrations of cannabinoids before meal times
- Profiles cannabinoids in the blood stream after the dose
- Examines the impact on appetite and related symptoms
- Examines impact on quality of life.

For people with cancer, the pathways that promote appetite are disrupted.

Their quality of life is reduced due to fatigue, low mood, nausea and insomnia – aspects critical to health and wellbeing.

Refer to:
Pain
clinical data

• THC * /CBD * is effective in chronic cancer pain relief alone and when added to standard opioid therapy.

• THC may target the affective quality of pain, instead of simply reducing pain intensity. CBD may modulate the effects of THC.

• The interactions between THC and CBD highlights the complexity of studies on cannabinoid-based drugs.

• For cannabis flos, specifically, the potential synergy of the cannabis terpene compounds define the final effect of the drug.

• Specific concentrations of THC or CBD, alongside subtle differences in plant composition may significantly affect the drug’s ability to treat specific medical conditions.

* THC delta-9-tetrahydrocannabinol;  
* CBD: cannabidiol

Reference:
According to WHO, if cancer pain occurs, there should be prompt oral administration of drugs in the following order:

- non-opioids (aspirin and paracetamol);
- then, as necessary, mild opioids (codeine);
- then strong opioids such as morphine, until the patient is free of pain.

Is it appropriate and justified to add cannabinoids?

It is appropriate and justified to substitute with cannabinoids?

Reference: www.who.int/cancer/palliative/painladder/en/
Pharmaceutical quality

Cultivation (GAP and GMP)

GAP: good agricultural practice  |  GMP: good manufacturing practice

Production – finished dose manufacture (GMP)

Quality specifications

- certificate of analysis from accredited lab
- consistent API content batch-to-batch
- no heavy metals or pesticides
- microbial content at acceptable levels

Dose forms

- vaporization (via medical device)
- oral

Internationally, the quality of medicinal-cannabis products can vary greatly

References:

GW Pharmaceuticals (UK)

Sativex: THC:CBD extract
Prescription medicine
Admin: sublingual spray

Epidiolex: CBD
Admin: oral dose

Bedrocan BV (NT)

Bedrocan: GMP cannabis flos
Prescribed medicine (NL)
Admin: vaporization
(oral dose forms also available)

AbbVie Inc. (USA)

Marinol: synthetic THC (Dronabinol)
Prescription medicine
Admin: oral dose

Valeant Pharma. Int. (USA)

Cesamet: synthetic THC (Nabilone)
Prescription medicine
Admin: oral dose
Administration

The four most common ways medicinal-cannabis is taken by patients across the world.

Vaporization

The most efficient route of administration is inhalation

The use of a vaporizer medical device avoids the respiratory disadvantages of smoking

### Vaporization

<table>
<thead>
<tr>
<th><strong>Administration</strong></th>
<th>Absorption via the lungs may reduce total daily intake.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose type</strong></td>
<td>Cannabis flos is used in granulated (ground up) form. A vapour of therapeutic cannabinoids and terpenes is inhaled</td>
</tr>
<tr>
<td><strong>Onset</strong></td>
<td>First effects can be noticed within minutes.</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>Typically between 2 - 4 hours.</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>Harmful compounds are virtually absent.</td>
</tr>
</tbody>
</table>

- **Fully standardised, pharmaceutical-quality cannabis flos provides an optimal medicinal product for vaporization and inhalation into the lungs.**

- The vapour of cannabis flos contains therapeutic levels of cannabinoids and terpenes. Harmful compounds are virtually absent, making it suitable for use by immune-compromised patients.

- The vapour content is rapidly absorbed by the lungs, improving the ability to adjust dose and therefore minimize side effects. There are no pyrolytic compounds that constitute a risk for second-hand exposure.
Vaporization developments

Raw Cannabis

- Constant Cannabinoid Levels
- Pharmaceutical-Grade

Structural Modification

- No Chemical Alteration
- No Added Excipients

Preloaded Cartridges

- Uniquely Identified
- Child Proof

Metered-Dosed Delivery

- 100 Microgram Resolution
- Selective Dosing
Where New Zealand is at:

- Guidelines for access and use – see Ministry of Health website
- Case-by-case basis
- Sativex™ registered for MS spasticity – predominantly prescribed off-label
- Other pharmaceutically derived products will be accessible

Not a panacea

A long human experience with cannabis
Among others, the following are widely believed, but are they right?

• “It is safe ...no one has ever died!”
• “People should just grow their own medicine!”

This is a new class of medicines

• There is evidence to suggest that medicinal cannabis has a role in palliative care.

• There is still more to understand – particularly use in very young children.

• There exists a risk of drug-drug interactions – especially within complex disease states employing a range of medications.

• Caution advised with a familial history of psychosis, and those with heart disease.
Further reading

Administration


Patient use surveys


Clinical reviews
