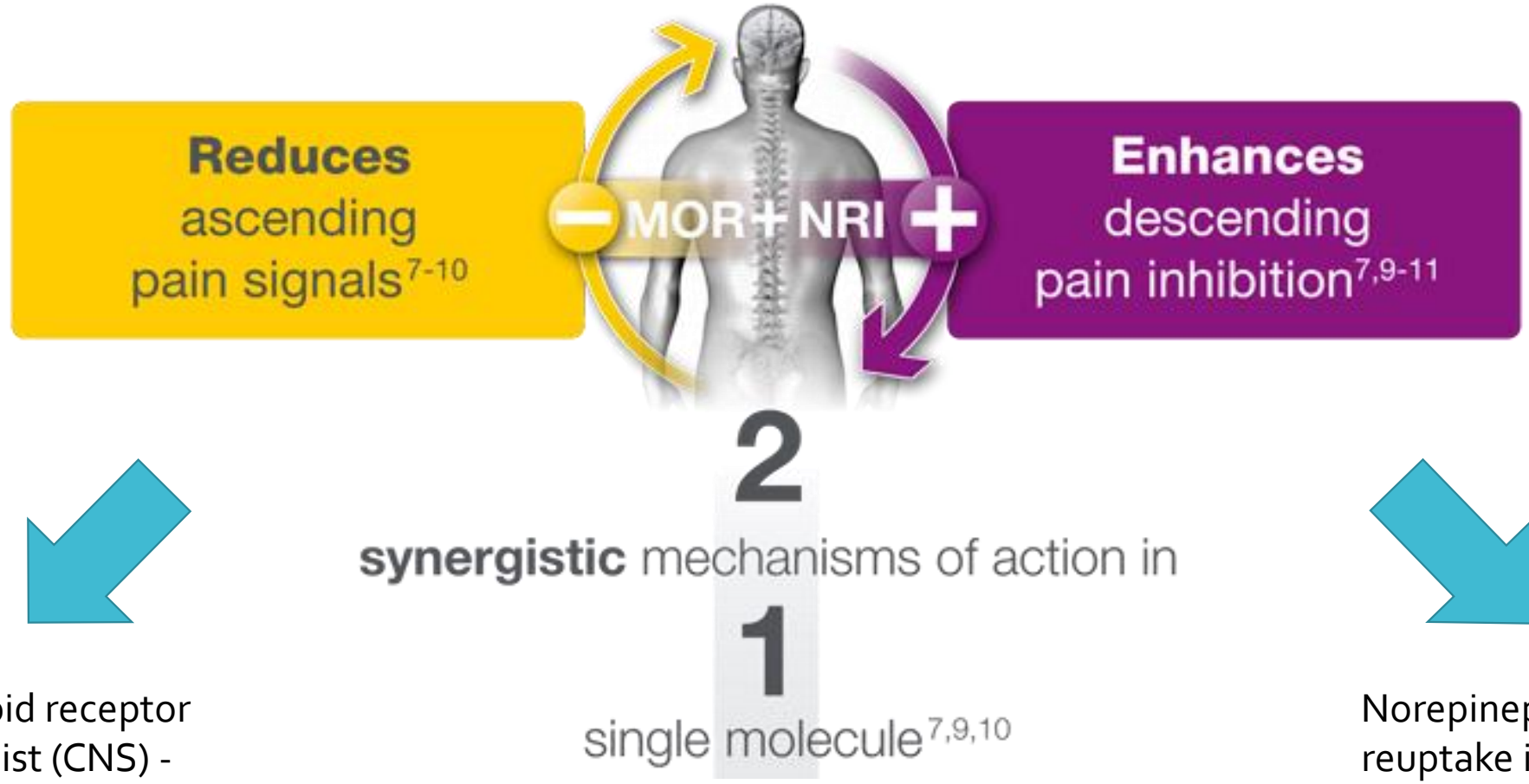
Emerging Analgesic Agents

Peter Langron

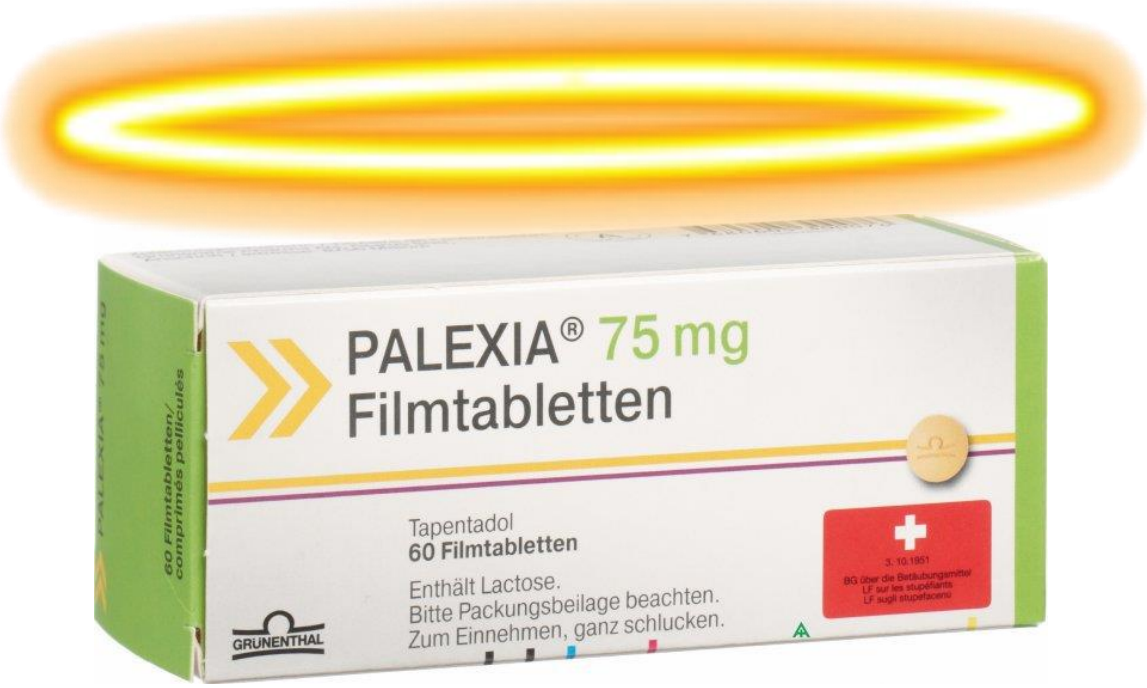
Anaesthetic Registrar

Tapentadol (Palexia)



mu-opioid receptor antagonist (CNS) - low affinity

Norepinephrine reuptake inhibitor (CNS and spinal cord)



Benefits:

- Synergistic mechanism
- Less GI side-effects
- Less genetic variation in metabolism – more predictable
- Lower risk of serotonin syndrome
- Lower abuse potential
- Less concern of tolerance and withdrawal

Tapentadol

Adverse effects:

- Nausea (30%)
- Dizziness (24%)
- Somnolence (15%)
- Itch
- Dry mouth
- Reduced seizure threshold

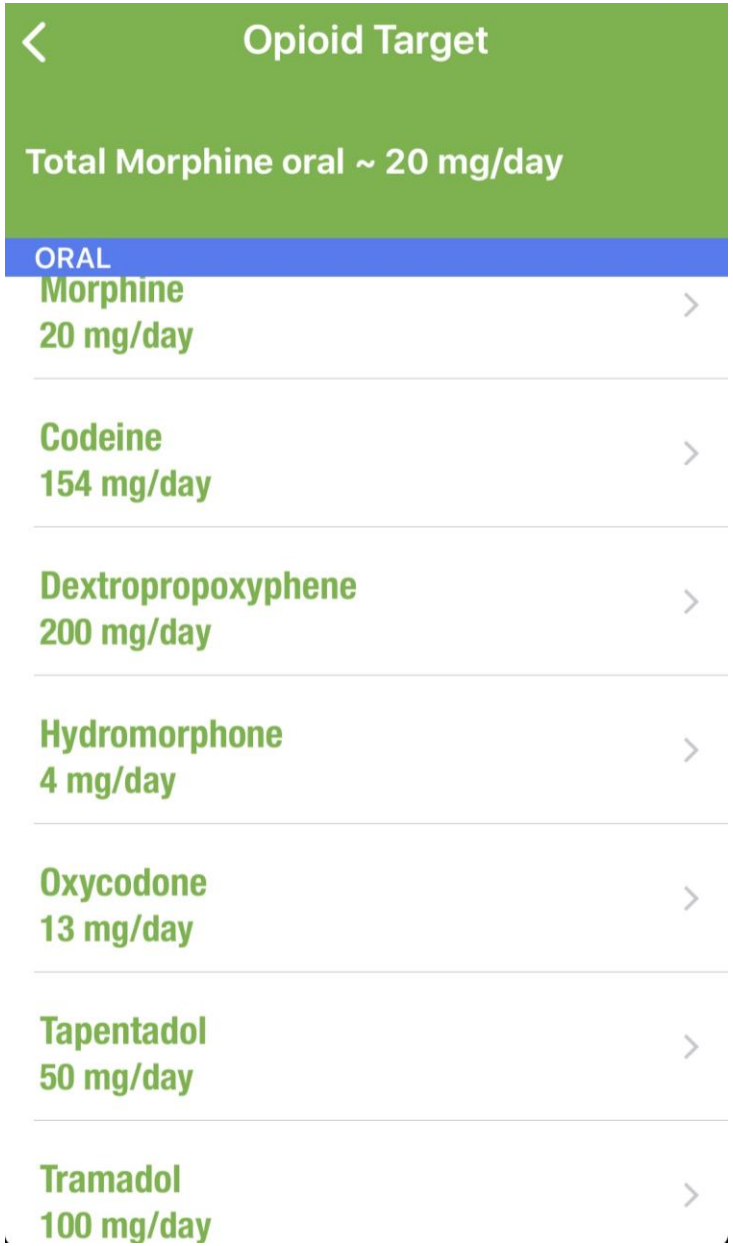
Synergistic effect with Monoamine Oxidase Inhibitors

Toxicity in hepatic impairment

Potential for abuse/dependence

Dosage


OPIOID
FPM ANZCA


Opioid Target
Total Morphine oral ~ 20 mg/day
ORAL
Morphine
20 mg/day
Codeine
154 mg/day
Dextropropoxyphene
200 mg/day
Hydromorphone
4 mg/day
Oxycodone
13 mg/day
Tapentadol
50 mg/day
Tramadol
100 mg/day

Pharmacokinetics

- Oral administration (IR and SR)
- Large volume of distribution (7.7L/kg)
- Hepatic Phase II metabolism (CYP2C9/CYP2C19)
  - Inactive metabolites
  - Extensive first-pass metabolism
- 99% renal excretion, 1% hepatic excretion
  - 3% excreted in urine as unchanged drug

Use in CKD

- Moderate-severe pain unresponsive to non-narcotic analgesia
- Neuropathic pain
  - Diabetic peripheral neuropathy
  - Peripheral vascular disease
- Cancer pain

- No dose adjustment needed for CrCl > 30 ml/min
- Not recommended for CrCl < 30 ml/min
  - No controlled efficacy studies
  - AUC of tapentadol-O-glucuronide increased 5.5x in severe renal impairment
  - Effect of metabolite accumulation is unknown

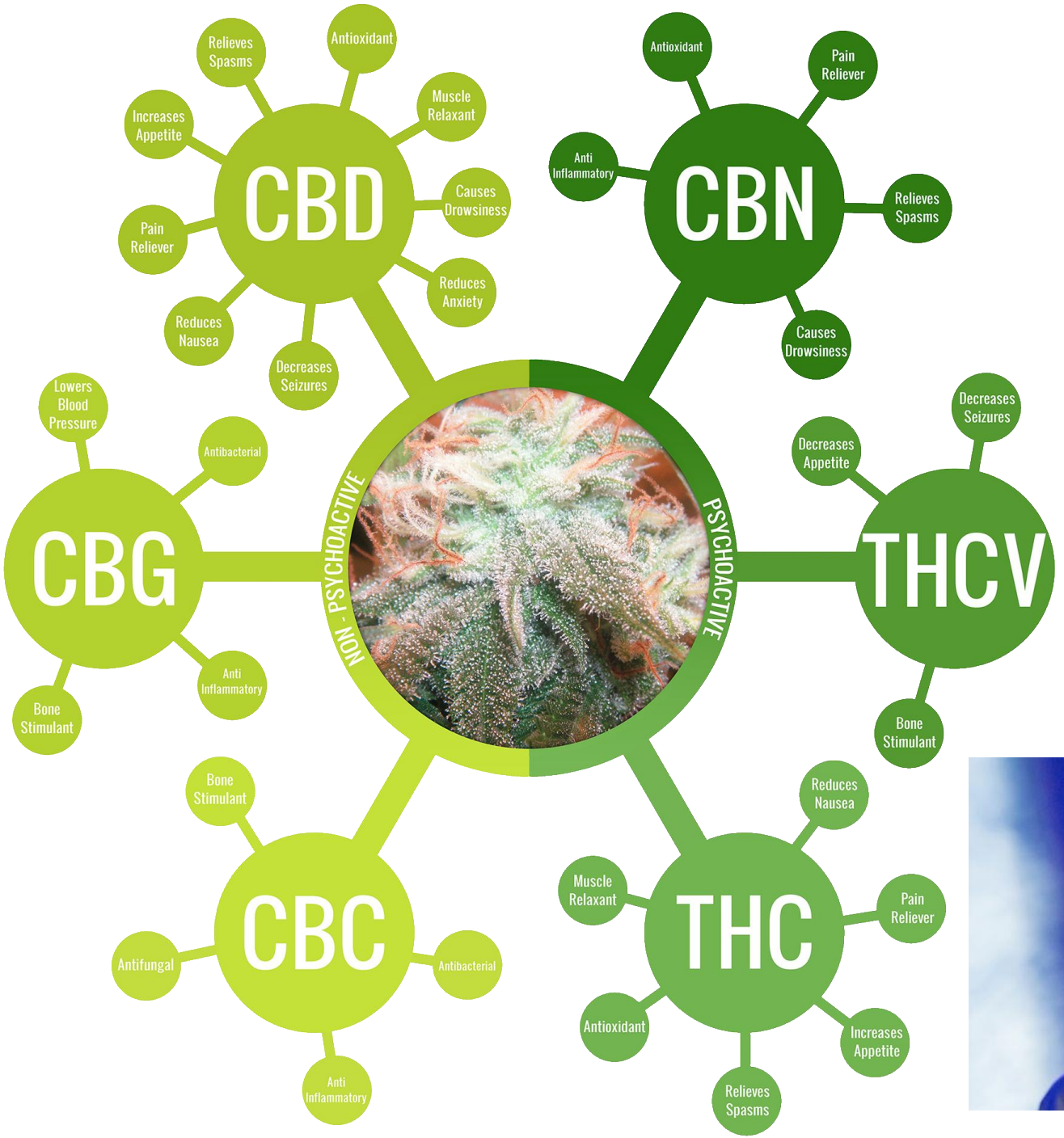
Dialysis

Table 1. Physical-Chemical Characteristics of Opioids Impacting Ability to Dialyze

Drug	Volume of Distribution (L/kg)	Plasma Protein Binding, %	Water Solubility[a]	Molecular Weight, g/mole
Methadone HCl	3.8	89	12:1	345.9
Fentanyl HCl	6	80	40:1	528.6
Hydromorphone HCl	1.22	N/A	03:1	321.8
Oxycodone HCl	2.6	45	06:1	405.9
Oxymorphone HCl	N/A	10	1-10:1[b]	337.8
Tapentadol HCl	7.7	20	1-10:1[b]	257.8

Medicinal Cannabis

Cannabidiol (CBD)



Tetrahydrocannabinol (THC)

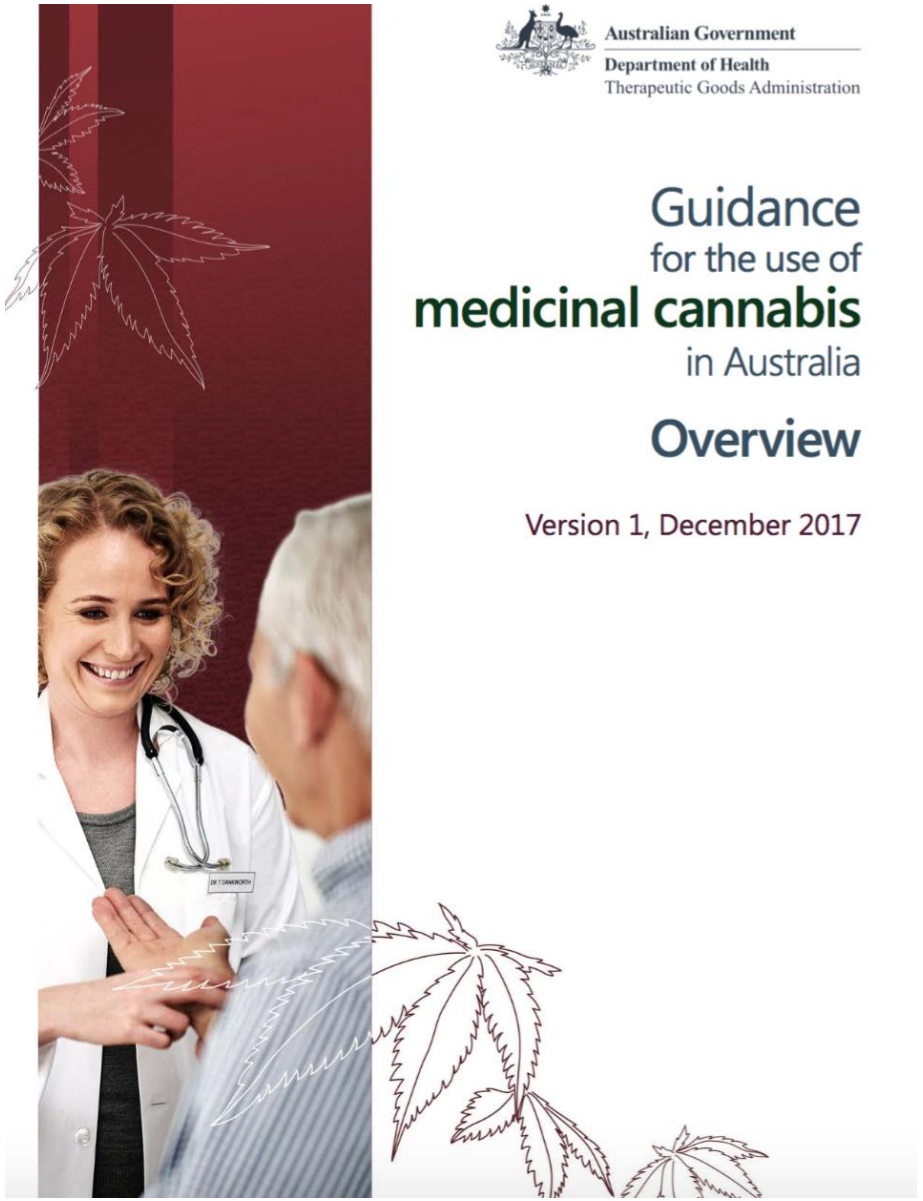
Formulations:

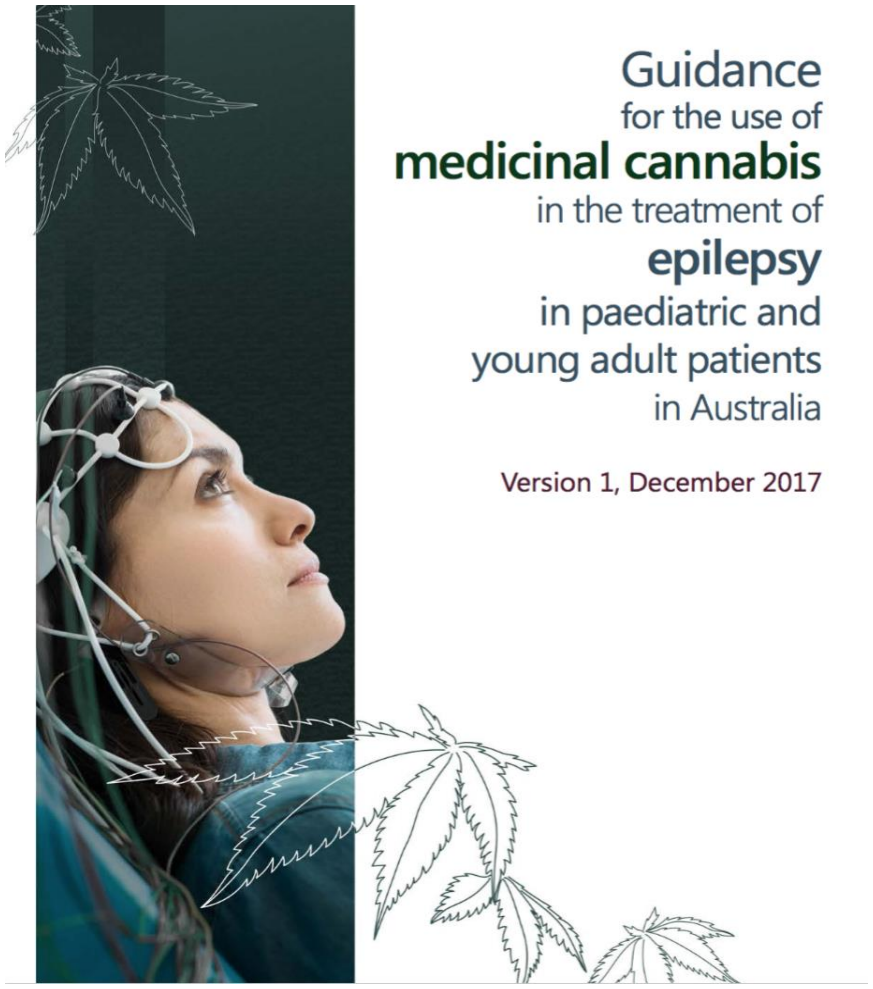
- Smoking
- Vaporising
- Oral (oil, liquid capsules)
- Oromucosal
- Topical

Variable CBD:THC ratios

The evidence

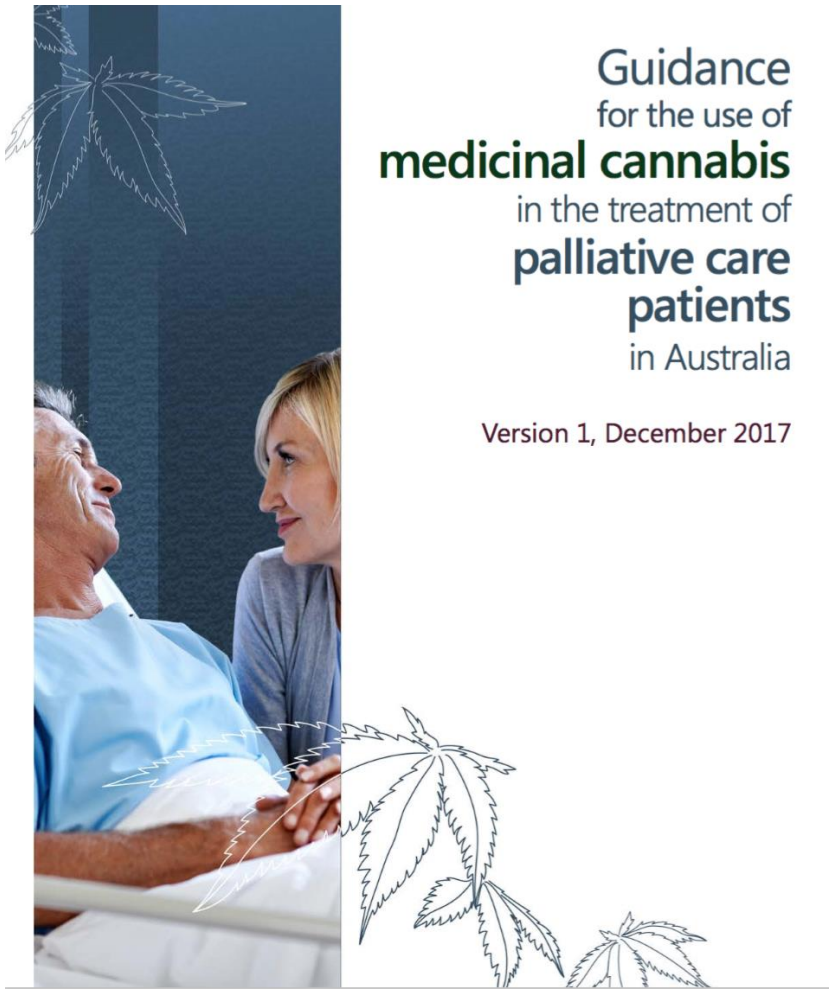
The evidence



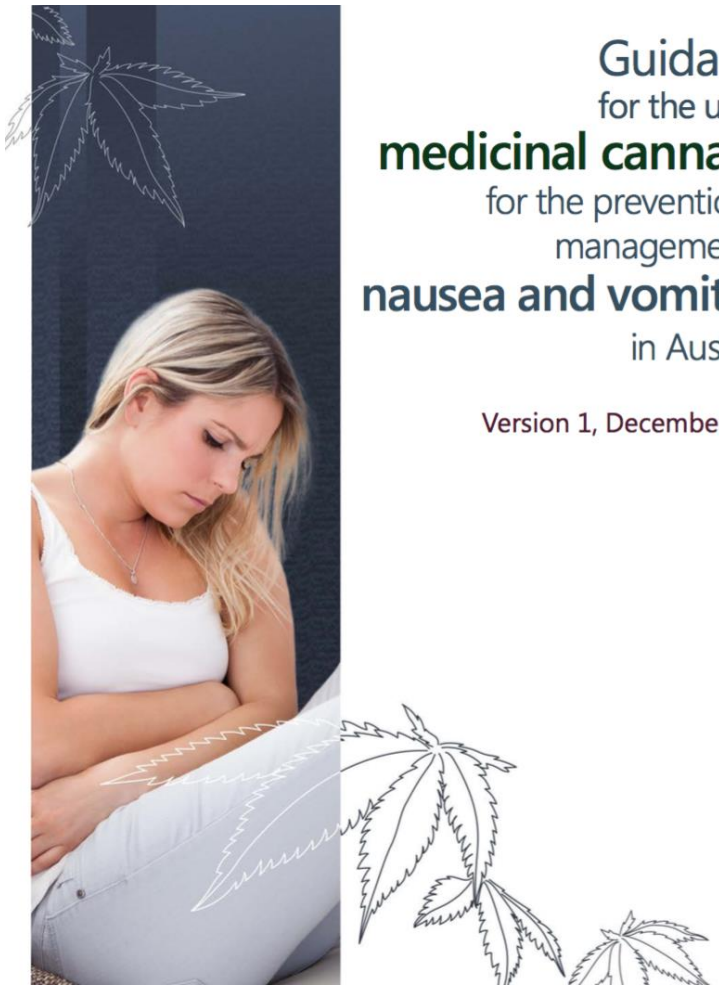


- Reduction in seizure frequency
- Improvement in quality of life
- Higher rates of adverse events
- Use as adjunct to conventional therapy

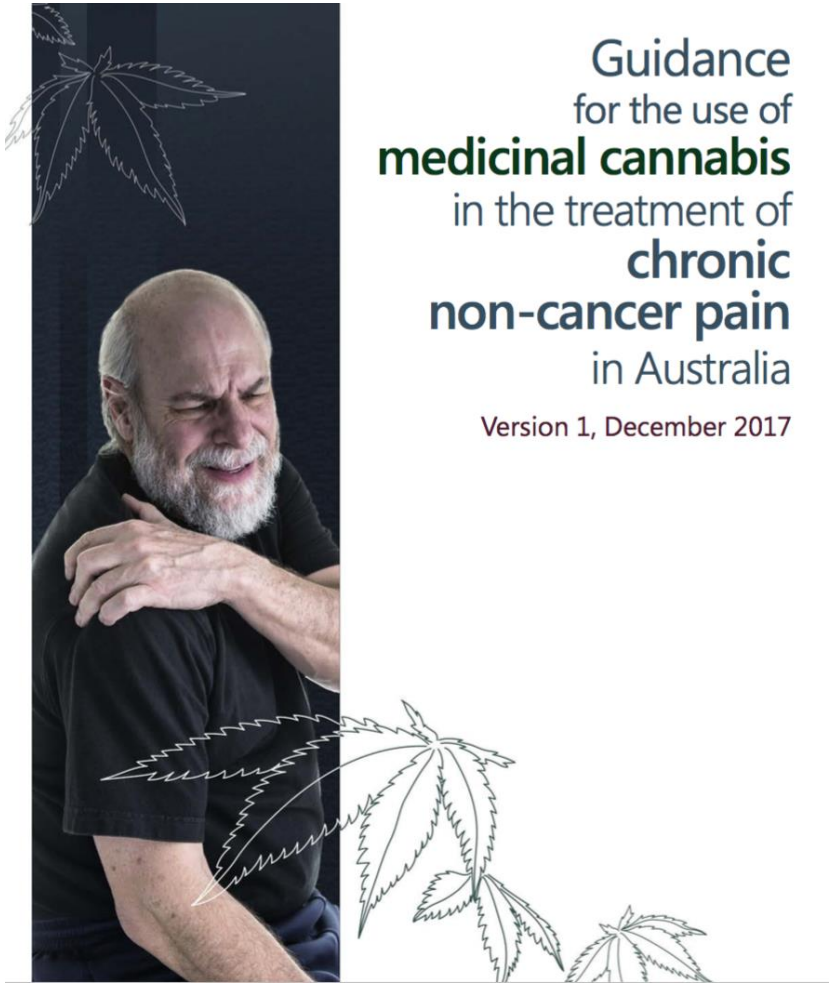
- Pain
- Spasticity
- Quality of life
- Side effects
- Use as adjunct



- Limited evidence for use in Alzheimer's Disease
- Little evidence for use in cancer symptoms
  - Appetite
  - Weight gain



- As effective as older antiemetics in chemotherapy-induced N&V
  - Not compared against newer agents
- No evidence for use in any setting



- Moderate evidence for reduction in pain scores for:
  - Multiple sclerosis
  - Neuropathic pain
- No evidence for arthritis/fibromyalgia
- Potential opioid-sparing effect in chronic non-cancer pain

Adverse events

- Unwanted effects include:
  - Dizziness/vertigo
  - Somnolence
  - Diarrhoea
  - Euphoria/dysphoria
  - Psychological dependence (10%)
- Patients in treatment groups twice as likely to withdraw from studies due to adverse events
  - Lack of long-term studies
- Concerns re safety of smoked and vaporised cannabinoids

Effect of cannabis use in people with chronic non-cancer pain prescribed opioids: findings from a 4-year prospective cohort study

Gabrielle Campbell, Wayne D Hall, Amy Peacock, Nicholas Lintzeris, Raimondo Bruno, Briony Larance, Suzanne Nielsen, Milton Cohen, Gary Chan, Richard P Mattick, Fiona Blyth, Marian Shanahan, Timothy Dobbins, Michael Farrell, Louisa Degenhardt

Use in CKD

- No studies looking at use in significant renal impairment, however…
- CBD and THC highly lipophilic – stored in fatty tissue for up to 4 weeks
- Metabolised in the liver (CYP2D6)
  - Several psychoactive metabolites
- 1/3 of parent drug and metabolites excreted in urine
  - Remainder in faeces

Use in CKD

- CB1 and CB2 receptors in kidneys
- Mechanisms of receptors involvement in pathology is unknown
  - Beneficial and deleterious effects
- ?new target for treatment of CKD
  - Improve renal function
  - Anorexia/cachexia
  - Pruritis
  - Nausea and vomiting