

Overview of Reviews of the evidence on medical uses of cannabis and cannabinoids

1 International Evidence

2 Evidence for Practice in Australia

A summary of findings

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Key Questions

- Do cannabis and/or cannabinoids have medical uses?
 - If so, for what medical conditions?
 - Which cannabinoids or cannabis preparations?
 - NB: did not produce guidance on clinical use
- One part of a much larger task:
 - Also reviewed evidence on adverse effects of recreational use
 - Made recommendations to improve the evidence base on:
 - Health effects
 - Medical uses
 - Cannabis policy evaluation

NAS approach to the evidence

- Review of systematic reviews and meta-analyses
 - Cochrane Collaboration reviews
 - Peer reviewed reviews e.g. Whiting et al, 2015
 - New papers since last published review
- If no good quality systematic reviews
 - Examined primary research studies
- Evidence synthesis
 - Using GRADE criteria

Evidence Matrix

US National Academy of Science, 2017

Strength of evidence on efficacy	RCT evidence on efficacy from	Support from other studies	Chance, bias, confounding
Conclusive	Strong study designs	Many studies; no opposing findings	Can be ruled out with reasonable confidence
Substantial	Strong study designs	Several studies; no opposing findings	Cannot be ruled out but minor role
Moderate	Some studies	Several studies; no opposing findings	Cannot be ruled out with confidence
Limited	Weak study designs	Mixed findings from other studies	Significant uncertainty re bias, confounding
Insufficient	None or evidence weak	Mixed findings or none	Substantial concerns re bias, confounding

Conditions reviewed by NAS 1

- Any medical condition which
 - cannabis or cannabinoids had been used to treat
 - in any US state which legally allowed medical use
 - A total of 24 health conditions
- Relief of symptoms
 - Pain acute and chronic of various causes
 - Nausea and vomiting caused by cancer chemotherapy
 - Appetite stimulation in HIV/AIDS patients
 - Anorexia nervosa and cancer patients
 - Spasticity and neuropathic pain in
 - multiple sclerosis
 - Spinal cord injury

Conditions reviewed by NAS 2

- Cancer:
 - Gliomas
- Gastro-intestinal disorders
 - Irritable bowel syndrome
- Neurological conditions
 - Epilepsy
 - Amyotrophic Lateral Sclerosis
 - Huntington's Chorea
 - Parkinson's Disease
 - Dystonias

Psychiatric conditions reviewed 3

- Depression
- Anxiety disorders
- Post Traumatic Stress Disorders
- Schizophrenia and psychoses

Key terms

- Cannabis: any product of *cannabis sativa*
 - Marijuana: flowering tops
 - Hash: compressed resin
 - Cannabis infused edibles and drinks
- Cannabinoids with potential medical use:
 - Pure drugs found in the cannabis plant: THC and CBD
 - Medicinal cannabis extracts e.g. Sativex, Epidiolex
 - Synthetic drugs that act on CB1 and CB2 receptors

Cannabinoids: approved and under trial

- Dronabinol (Marinol) synthetic THC
 - Approved for chemotherapy-induced nausea & vomiting
 - Appetite stimulation in HIV/AIDS
- Nabilone: a synthetic THC agonist
 - Approved in USA for CINV and appetite stimulation
- Nabiximols:
 - Sativex approved for muscle spasticity in MS
- CBD-based cannabis preparation
 - Epidiolex: seeking approval for epilepsy

Chemotherapy-induced Nausea and Vomiting in Cancer Patients

- Reviews of RCTs show THC
 - Better than placebo and as good as prochlorperazine
 - Few comparisons with newer drugs
 - Few studies of smoked cannabis
- Adverse events
 - somnolence; dizziness, anxiety etc
- Synthesis:
 - Conclusive evidence of efficacy
 - Cochrane review: moderate evidence of efficacy

Wasting Syndrome & Anorexia

- Cannabis in AIDS-related wasting in late 1980s
 - limited evidence from clinical trials for THC
 - 4 trials in total of 300 patients
- Dronabinol approved by FDA for this indication
 - very limited use because dose titration difficult & side effects
 - Very little need after the advent of HAART
- NAS and Cochrane both concluded:
 - weak evidence of efficacy
 - possible role as an adjunctive treatment (Cochrane)

Analgesia

- Animal evidence of analgesic effects
 - different mechanisms to opioids
 - potential for adjunctive use & synergistic effects
- Moderate support for efficacy in clinical trials
 - Neuropathic pain MS using nabiximols the best studied
 - Modest efficacy compared to placebo
- Systematic reviews
 - NAS: substantial evidence but modest analgesic benefit
 - Cochrane: moderate evidence in neuropathic pain in MS

Spasticity in Multiple Sclerosis

- Substantial self-reported evidence for efficacy:
 - Primarily RCTs of nabiximols (Sativex)
 - Subjective benefit and patient preference for nabiximols
 - But limited objective evidence of improvement
- Systematic evaluation consensus
 - Whiting et al (2015); NAS (2017); Cochrane
 - Substantial evidence of subjective benefit
 - Less evidence of objective benefit

Epilepsy

- Anticonvulsant effects in animal models of epilepsy
- Case reports of benefit in children with epilepsy
- Open label US study in 137 children
 - 36% reduction in seizure frequency
- RCTs completed but not yet published
- Evaluation consensus: NAS, Whiting and Cochrane
 - Limited evidence
 - Worth conducting RCTs

Other medical indications

- Irritable bowel syndrome
- Neurological disorders
 - Parkinson's disease
 - Huntington's disease
 - Amyotrophic lateral sclerosis
 - Dystonias
- NAS synthesis of the evidence
 - Limited or insufficient to draw conclusions

Psychiatric indications

- Psychiatric disorders
 - Anxiety disorders
 - Post-traumatic stress disorders
 - Depression
 - Schizophrenia (CBD)
- NAS concluded for all of these
 - Limited or insufficient to draw any conclusions

Summary of Conclusions

- Oral cannabinoids are effective anti-emetics in adults
- Cannabis & cannabinoids reduce chronic pain in adults
- In adults with MS-related spasticity, short-term oral use of cannabinoids improves patient-reported spasticity
- For all these conditions the effects “are modest”
- For all other conditions “inadequate information to assess their effects.”

Review commissioned by Australian Federal Government

- NAS a review of reviews
 - Done under time pressure as part of a larger review
 - Relied on a small number of systematic reviews
 - Did not provide any guidance on clinical use
- What we are doing :
 - Detailed reviews of primary studies for major indications
 - Look for study evidence to inform clinical use
 - Include evidence from RCTs now in progress
 - Summarise clinical guidance in other jurisdictions

Progress to date 1

- Reviews of reviews for meeting in February
 - Epilepsy
 - Palliative care
 - Chronic pain
 - Multiple sclerosis
- *Precis* of National Academy of Science review

Progress to date 2

- Reviews of primary studies done for:
 - Epilepsy
 - Palliative care
- Reviews reviewed by clinical experts in field
- Guidance documents for 19th May meeting
 - Drafted for Epilepsy and Palliative care
 - Based on reviews and published guidance
 - Seeking expert comment on drafts
 - Will be considered at May meeting by experts

Where to next?

- Reviews of primary research studies for:
 - Multiple sclerosis
 - Chronic pain
 - To be reviewed by clinical experts in field
- Guidance documents for later meetings
 - Based on reviews and published guidance
 - Revised in light of expert comments on drafts