NDARC
National Drug & Alcohol Research Centre

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UNSW AUSTRALIA

# Cannabis and cannabinoids for medicinal purposes

International Evidence and Evidence for Practice in Australia

Medicine | National Drug and Alcohol Research Centre

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# Key Questions

New Federal Government Legislation November 2016 to make Medicinal Cannabis available for appropriate patients

Need for Evidence Framework and Guidance to support the drafter legislation

# 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 |

# Project Background and Aims

- October 2016:
  - NDARC contracted to review evidence
    - On the medical use of cannabis and cannabinoids
    - For key medical conditions (project until end 2017)

- Aim to provide an evidence summary to assist:
  - Individual clinicians
  - State and Territory health Departments and
  - The Commonwealth Department of Health

# 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

# Activity 1

- Review of critical reviews of evidence (5 conditions)
- Pain, Epilepsy reviews presented here
- Multiple Sclerosis, Palliative Care and Nausea and Vomiting also completed but not presented today but results briefly summarised verbally

- Review of existing clinical guidance documents and guideline development approaches

# Activity 1 Updates

# Pain

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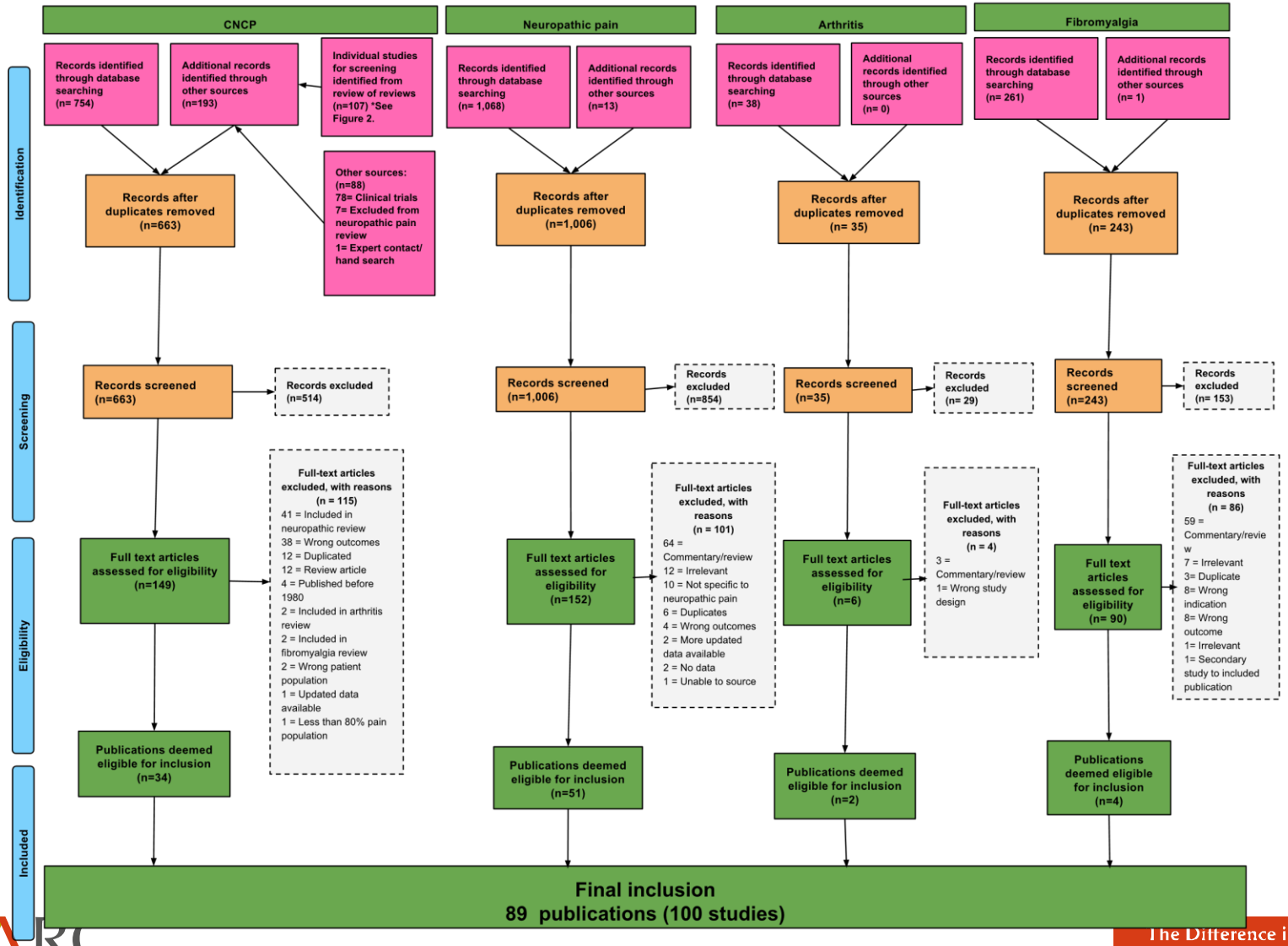
Michael Farrell
Louisa Degenhardt
Expert: Dr Bridin Murnion

# Search results



# Included studies

- 89 publications comprising 100 individual studies
- Comprising:
  - 24 parallel RCTS
  - 23 cross-over RCTs
  - 53 observational studies
    - 25 open-label studies
    - 9 prospective/cohort studies
    - 9 cross-sectional or retrospective surveys
    - 4 retrospective chart reviews
    - 6 case series and N-of-1 studies

# Outcomes

As per IMMPACT recommendations for outcomes:

| Domain | Measures |
|---|---|
| **Pain intensity** | • 30% reduction in pain<br>• 50% reduction in pain<br>• Reduction in pain scores |
| **Withdrawals** | • All-cause<br>• Adverse event-related |
| **Adverse events (AEs)** | • All-cause<br>• Serious<br>• Treatment-related (TAE)<br>• Specific AEs |
| **Physical functioning** | • Global functioning<br>• Quality of life<br>• Sleep |
| **Emotional functioning** | • Anxiety<br>• Depression |
| **Participant ratings of global improvement** | • PGIC |

# Characteristics of included studies (*n*=100)

- **Pain condition**:
  - 45 neuropathic pain
    - 13 MS-related; 32 non MS-related
  - 8 Fibromyalgia
  - 1 Arthritis (rheumatoid)
  - 46 CNCP
    - 13 MS-related; 31 non MS-related

# Characteristics of included studies (*n*=100)

- **Cannabinoid product**:
  - 25 Cannabis sativa
  - 24 Nabiximols
  - 17 Dronabinol
  - 17 Nabilone
  - 11 THC extract
  - 3 THC:CBD extract
  - 2 CBD extract
  - 1 Ajulemic acid
  - 2 unclear
- 71 were **pharmaceutical grade** (19 were not; 12 unclear)
- 81 were secondary in **therapeutic hierarchy** (4 primary; 17 unclear)

# Epilepsy

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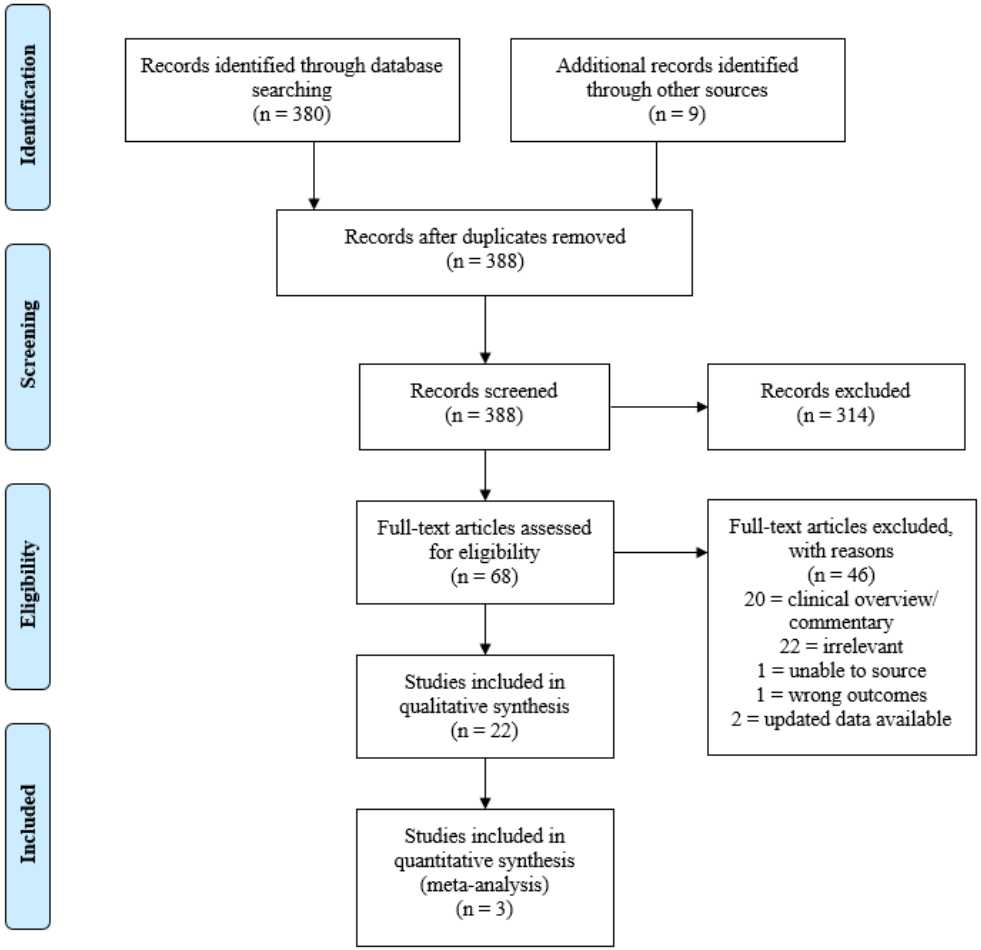
Expert: Associate Professor Geoffrey Herkes

# Findings: Epilepsy

- Study-level search - 383 articles
  - Clinical trials and observational studies
  - 314 articles excluded
  - 62 articles full text screening
  - 22 studies extracted
    - 5 randomised controlled trials (3 studies for meta-analysis)
    - 4 non-randomised clinical trials
    - 13 observational or self-report studies



# Outcomes: Epilepsy

- Complete seizure freedom
- 50% or greater reduction in seizure frequency (responder rate)
- Quality of life outcomes
- Withdrawals – adverse events or any reason
- Adverse events
- Serious adverse events

# Products and dosages

| Cannabinoid | Commercial or pharma product names | Dose range | Delivery form and method |
|---|---|---|---|
| CBD | Epidiolex; Rheem Oil | RCT: 20mg/kg/day Observational: 2-50mg/kg/day | Oral – capsule or oil |
| CBD:THC | Charlotte's Web | 1-28mg CBD/kg/day: 0.1-0.7 mg THC/kg/day | Oral – oil |
| THC | | 0.07-0.14mg/kg/day | Oral – oil or tincture |
| Cannabis sativa | | 0.5-8.0g/day | Smoked, vaporised or drunk |

# Meta-analysis results

In 3 RCT studies, CBD was significantly better than placebo at:

- Achieving complete seizure freedom
- Seizure reduction of 50% or more
- Improved quality of life

In comparison to placebo, patients were significantly more likely to:

- Withdraw from the trial
- Experience adverse events (especially SAEs)

# Conclusions: Epilepsy

- Limited RCTs indicate there may be therapeutic benefit of CBD in treating epilepsy and seizures – both seizure freedom and significant reduction in seizures
- CBD relatively well tolerated; evidence for THC and CBD:THC products are all observational
- Observational trials are positive, but many limited by lack of control and data on dosing
- Safety issues: dosing, product concentrations, interactions with other medications, non-medically supervised delivery

# Activity 2

- Conduct & publication of study-level systematic reviews (7 conditions)
- Drafts of clinical guidance for consultation

# Guidance development

# Aims of guidance document

- Overview of current evidence (based on reviews)
- Grade strength and quality of evidence
- Use of cannabinoid products
  - Forms, routes and standardisation
  - Dose
  - Place in therapeutic hierarchy
- Prescriber considerations
  - Tolerability of treatment, adverse events
  - Evidence on time to response
  - Recommended process for auditing outcomes

# Where to next

TGA and National Legislation keen to ensure that patients have access to medication consistent with the newly drafted legislation.

Guidance documents now in further consultation and drafting with assistance of Clinician Expert Networks

Complex balance between different stakeholders and differing interpretations of the current evidence.

Classic need to straddle broad range of views