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Medicinal Cannabis

Snapshot Review

A review of recent evidence for the use of medicinal cannabis, in particular for the treatment of chronic pain, mental health, and nausea.

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A joint initiative of WorkSafe Victoria and Monash University

CONTENTS

LIST OF TABLES

LIST OF FIGURES

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Disclaimer: This Snapshot Review has been produced by the Institute for Safety, Compensation and Recovery Research (ISCRR) in response to a specific question from WorkSafe Victoria. The content of this report does not involve an exhaustive analysis of all existing evidence in the relevant field, nor does it provide definitive answers to the issues it addresses. The review findings were current at the time of publication, April 2020. Significant new research evidence may become available at any time. ISCRR is a joint initiative of WorkSafe Victoria and Monash University. The opinions, findings and conclusions expressed in this publication are those of the authors and not necessarily those of WorkSafe Victoria or ISCRR.

ABBREVIATIONS

Table 1. *Abbreviations*

Abbreviation	Details
ACCS	Accident Compensation Conciliation Service
AE	Adverse Event
AMSTAR	Assessment of the Methodological quality of Systematic Reviews
CBD	Cannabidiol
CBM	Cannabis-based medicines
CI	Confidence Interval
CNCP	Chronic non-cancer pain
DSM-V	Diagnostic and Statistical Manual of Mental Disorders - V
FDA	Food and Drug Administration
FPM	Faculty of Pain Medicine
GRADE	Grading of Recommendations Assessment, Development and Evaluating
MS	Multiple Sclerosis
NASEM	National Academies of Sciences, Engineering and Medicine
NeNETS	Non-Established, New or Emerging Treatments and Services
NHMRC	National Health and Medical Research Council
NIH	National Institutes of Health
OR	Odds Ratio
PTSD	Post-Traumatic Stress Disorder
RACGP	Royal Australian College of General Practitioners
RCT	Randomised controlled trial
RD	Risk Difference
RR	Risk Ratio
SCET	Standardised Cannabis Extract with THC
SMD	Standardised Mean Difference
SR	Systematic Review
SSRI	Selective serotonin reuptake inhibitors
TGA	Therapeutic Goods Administration
THC	Tetrahydrocannabinol
WHO	World Health Organisation
WSV	WorkSafe Victoria

EXECUTIVE SUMMARY

Background

Since the Victorian Government legalised medicinal cannabis for patients in exceptional circumstances in 2016, WorkSafe agents have received over 20 requests to fund medicinal cannabis for the treatment of pain, mental illness and nausea. These requests have been managed in line with the Non-Established, New or Emerging Treatments and Services (NeNETS) policy which requires Level I or II National Health and Medical Research Council (NHMRC) evidence to support the use of a treatment that has not yet been assessed by the relevant federal regulatory body.

Purpose

WorkSafe Victoria (WSV) sought an Evidence Review to identify whether any new Level I/II evidence for the use of medicinal cannabis had been published since end 2016 that shows whether it is safe and effective, in particular for the treatment of chronic non-cancer pain (CNCP), mental health problems, and nausea.

Results

We identified 17 systematic reviews published between November 2016 to March 2020.

Chronic Pain. There was Level I evidence that medicinal cannabis may be effective for reducing general chronic and nociceptive pain. For neuropathic pain results around effectiveness were discordant (Level I evidence). Where indicated as effective, the therapeutic potential of medicinal cannabis was limited by its marginal decreases in pain compared to placebo, and small response rate. Despite there being some Level I evidence, there were significant limitations to the quality of the available evidence (e.g., high risk of bias, small studies), which together with safety concerns (e.g., risks for adverse events), questions the potential therapeutic benefits of medicinal cannabis for these pain indications. Medicinal cannabis may be effective in reducing orthopaedic pain (Level IV evidence), but low-quality research and noted potential harms limits conclusions of efficacy. No evidence was identified to support medicinal cannabis as a treatment for headaches and migraines.

Mental Health. Medicinal cannabis may be effective (mixed Level I and IV evidence) for reducing symptoms of social anxiety disorder, but the certainty in this evidence is low. There is mixed/inconsistent Level I evidence on whether medicinal cannabis is effective for reducing symptoms of (general) anxiety disorder and post-traumatic stress disorder. Medicinal cannabis is unlikely to have any therapeutic benefit for depression (Level I evidence) and bipolar disorder (Level IV evidence), and could worsen symptoms in both indications. Medicinal cannabis was not associated with remission of any mental health disorders. In the mental health field medicinal cannabis is an emerging research area, characterised by a lack of well-controlled and high-quality studies focused on specific clinical populations.

Nausea. Medicinal cannabis may be effective for reducing chemotherapy-induced nausea and vomiting (Level I evidence). However, it should be noted that the reviews largely contained dated trials, and compared antiemetics which are no longer standard of care today.

Implications

In general, the field of medicinal cannabis was plagued by low quality evidence. It lacked long-term impact studies, and was only an emerging field of research in mental health. There were well-described potential harms and increased risks for adverse events, which raise questions around safety. Great variability in formulations, dosage, routes of administration and therapeutic range were noted, which

makes it challenging to draw firm and consistent conclusions around its efficacy. Thus, we conclude that its safety and efficacy is limited, particularly as first-line treatment for chronic pain, mental ill health, and nausea and vomiting.

At the time of writing, the findings of this Snapshot Review are in line with the current Level I and II evidence used by WSV.

1. INTRODUCTION

1.1 Background

Cannabinoids refer to chemical substances which link to the body's natural endocannabinoid system CB1 and CB2 receptors and consist of two main types: THC and CBD (see Appendix 1 for an overview on cannabinoids).

In April 2016, the Victorian Government legalised medicinal cannabis for patients in exceptional circumstances. They established the Office of Medicinal Cannabis within the Department of Health and Human Services to oversee manufacturing and all clinical aspects of the medicinal cannabis framework.

At the time of writing WorkSafe agents have received at least 20 requests to fund medicinal cannabis for the treatment of pain, mental illness and nausea. These requests have been managed in line with the Non-Established, New or Emerging Treatments and Services (NeNETS) policy, which requires Level I/II National Health and Medical Research Council (NHMRC) evidence to support the use of a treatment that has not yet been assessed by the Pharmaceutical Benefits Advisory Committee.

The NeNETS is a point-in-time database which continuously evolves based on current Level I and II evidence. At the time of writing there is some evidence supporting the efficacy of medicinal cannabis (cannabidiols only) in the management of neuropathic pain, in particular a 2017 systematic review by Aviram that found that "cannabis-based medicines might be effective for chronic pain treatment, based on limited evidence, primarily for neuropathic pain patients".[4] However, most studies into the effectiveness of medicinal cannabis for other conditions and neuropathic pain are considered to be methodologically flawed.

Special Access Scheme approvals by the Therapeutic Goods Administration (TGA) for medicinal cannabis have demonstrated an exponential increase, rising from 37 per month in February 2018 to 672 per month in January 2019. The rate of funding requests for medicinal cannabis to WorkSafe Victoria has also increased in frequency.

The position of the Faculty of Pain Medicine (FPM) on the use of medicinal cannabis, updated in February 2019, is "At the present time, the scientific evidence for the efficacy of cannabinoids in the management of people with chronic non-cancer pain is insufficient to justify endorsement of their clinical use".

The Royal Australian College of General Practitioners (RACGP), in a position statement published in 2019, stated that the need for "further high-quality research into the safety and effectiveness of medicinal cannabis products, as the current evidence is limited and inconclusive".

Access to medicinal cannabis obtains frequent media coverage, with community debate around medicinal cannabis often being emotive and sending mixed signals to the broader public regarding the appropriate use of medicinal cannabis. Public support and promotion by the Victorian Government into the cultivation of medicinal cannabis may also underpin community expectation that medicinal cannabis should be funded by WSV, regardless of the clinical indication or evidence base.

WSV sought an Evidence Review to identify whether any new Level I/II evidence for the use of medicinal cannabis shows whether it is safe and effective, in particular for the treatment of chronic pain, mental health problems, and nausea.

2. AIMS AND APPROACH

This project aimed to identify recent evidence for the use of medicinal cannabis in the treatment of workplace injuries, and compare it to data currently referenced by WSV in funding requests for medicinal cannabis. This was to:

1) Ensure workers have access to treatment that is safe and effective for their work-related injury.
2) Inform the application of the NeNETS policy to funding requests for medicinal cannabis.
3) Support WSV and Agents when decisions to deny funding for medicinal cannabis are disputed through ACCS or Medical Panels.

2.1 Approach

A snapshot review of current published systematic reviews relating to the use of medicinal cannabis in the treatment of pain, mental health conditions and nausea was conducted, with a search period of November 2016 to March 2020. Systematic reviews of randomised controlled trials (RCTs) are considered NHMRC Level I evidence. Systematic reviews containing studies other than RCTs are lower levels of evidence and have been included but indicated as such. The types of studies in each systematic review are indicated in text and tables, as well as the level of evidence.

Evidence used by WSV at the time of writing was also reviewed, and is summarised in Section 3.

Five databases were searched (PubMed, PsycINFO, ScienceDirect, Cochrane Library and Embase), using the following terms:

- medical cannabis (including variants such as medicinal cannabidiol, cannabinoid, marijuana) AND
- (systematic) reviews with a focus on chronic non-cancer pain, psychiatric or mental health (including psychopathology, Post-traumatic Stress Disorder (PTSD), depression, and anxiety), or nausea and vomiting.

A total of 439 articles were identified and screened for relevance and eligibility, which resulted in 17 systematic reviews meeting the inclusion criteria and included in this Snapshot Review. See Appendix 2 for inclusion and exclusion criteria. A section on the adverse effects of medicinal cannabis has been included, as well as the current known long-term outcomes, for consideration in the broader workplace/health context (see Section 7).

3. SUMMARY OF EVIDENCE CURRENTLY USED BY WSV

3.1 Chronic Pain (including neuropathic pain)

Current evidence used by WSV was reviewed (see Table 2).

We note a couple of limitations to the WSV data referenced:

- The National Academies of Sciences, Engineering and Medicine (NASEM) report concluded that plant-derived cannabinoids were more effective in reducing pain than the control agent, in particular for neuropathic pain.[5] This data has been scrutinised on the basis of:
  - Generalisation of findings from neuropathic pain to chronic pain[6]
  - Potential bias towards positively evaluating cannabis products and interpretation of statistical significance[6][7]
  - The 2018 NASEM update and similar analysis reducing confidence in strength of earlier findings.[8][9]
- The 2019 Royal Australian College of General Practitioners (RACGP) Position Statement noted there is some evidence for the treatment of neuropathic pain using medicinal cannabis. We note the following:
  - The overall effect size was small
  - The Statement incorrectly cited evidence from the Campbell et al. 2018 study where no participants were prescribed medicinal cannabis products.[10] Cannabis use was investigated in people living with chronic non-cancer pain who had been prescribed opioids, rather than specific treatment of pain using medicinal cannabis.

Table 2. *Summary - Medicinal Cannabis and Chronic Non-Cancer Pain*

Level I or II Evidence	Timeframe	Key outcomes/recommendations
FPM – Australia and New Zealand College of Anaesthetists – Statement on Medicinal Cannabis (2019)	Cites selected sources up to 2018 (including Stockings et al. 2018,[11] TGA 2017,[1] National Academies of Sciences, Engineering, and Medicine 2017,[5] etc.)	• Complexity of phenotype of CNCP noted. • Stated that at present, the scientific evidence for the efficacy of cannabinoids in the management of people with CNCP is insufficient to justify endorsement of clinical use.
TGA 2017 Guidance for the use of medicinal cannabis and cannabinoids in the treatment of CNCP[1]	1980 – early 2017	• Based on 102 studies (including 49 RCTs). • Reported moderate confidence that CNCP patients receiving medicinal cannabis were more likely to achieve 30% and 50% reductions in pain than patients given a placebo. • Evidence strongest for Nabiximols. Recommendations: • A comprehensive sociopsychobiomedical assessment of the patient with CNCP is appropriate. • The use of medications including medicinal cannabis is not the core component of therapy for CNCP. • Patient education is a critical component of therapy for CNCP, particularly around drug therapy expectations. • Larger trials of sufficient quality, size and duration needed to examine the safety and efficacy of medicinal cannabis use in CNCP.

Level I or II Evidence	Timeframe	Key outcomes/recommendations
Stockings et al. 2018 Systematic Review and Meta-Analysis[11]	1980 - July 2017	• Review of 104 studies (47 RCTs). • Across RCTs, pooled event rates (PERs) for 30% reduction in pain were 29.0% (cannabinoids) vs 25.9% (placebo); significant effect for cannabinoids was found. For 50% reduction in pain, PERs were 18.2% vs 14.4%; no significant difference was observed. • Estimated pooled rate of all-cause adverse events (AEs) was 81.2% for cannabinoid groups, compared with 66.2% of those receiving placebo. • Conclusion: Evidence for effectiveness of cannabinoids in CNCP is limited; unlikely that cannabinoids are highly effective medicines for CNCP; high rates of dropout from adverse events; long-term efficacy and safety is unknown.
Aviram & Samuelly-Leichtag (2017)[4]	Up to July 2015	• Review of 43 RCTs (2,437 patients) including 24 RCTs eligible for meta-analysis. • Limited evidence for pain reduction in chronic pain; moderate to good treatment effect for neuropathic pain. • Considerable incidence of adverse events for oral/ oralmucosal routes of administration (notably in central nervous (e.g., dizziness, drowsiness) and gastrointestinal systems). • Authors could not conclusively state that these results were clinically significant.
Campbell et al. 2018 Cohort study[10]	4th year follow-up Dec 2017	• Four-year prospective cohort study of 1,514 participants of which 295 had used cannabis for pain. • No evidence that cannabis use improved patient outcomes. • No evidence that it reduced pain severity, nor did it produce an opioid-sparing effect.
National Academies of Sciences, Engineering and Medicine (NASEM) cannabis evidence review (2017)[5]	1999 - 2016	• Patients who were treated with cannabis/cannabinoids more likely to experience a clinically significant ↓pain symptoms. • Effects of cannabinoids were modest.
RACGP Use of Medicinal Cannabis Products - Position Statement (2019)[2] – cites the Campbell 2018 Cohort study[10]	Up to 2018	• Evidence available for the treatment of neuropathic pain using medicinal cannabis products. • The magnitude of effect is small.

3.2 Mental Health

Evidence used by WSV at time of writing of this report (Table 3) indicated limited support for use of medicinal cannabis to treat PTSD symptoms, and an increased risk for developing schizophrenia and psychoses. The NASEM review indicated no greater likelihood of developing depression, anxiety or PTSD with regular cannabis use, but may increase risk of certain mental health conditions, symptoms and suicide ideation.[5] Cannabinoids have been found to decrease PTSD symptoms (sleep quality, frequency of nightmares).[12] Cannabinoids are not indicated by Phoenix Australia (Centre for Posttraumatic Mental Health) as treatment for PTSD who recommend psychological treatment as first line treatment, and selective serotonin reuptake inhibitors (SSRI) antidepressants where medication is considered.[13]

Table 3. *Summary - Medicinal Cannabis and Mental Health*

Level I or II Evidence	Timeframe	Key outcomes/recommendations
NASEM cannabis evidence review (2017)[5]	1999-2016	• Cannabis use likely to increase risk of developing schizophrenia and other psychoses; higher use = greater risk. • History of cannabis use may be linked to better performance on learning and memory tasks in individuals with schizophrenia/other psychoses. • Cannabis use does not appear to increase likelihood of developing depression, anxiety, and PTSD. • Individuals with bipolar disorder: near daily cannabis use may be linked to greater symptoms than non-users. • Heavy users more likely to report thoughts of suicide than non-users. • Regular cannabis use is likely to increase risk for developing social anxiety disorder.
Mizrachi Zer-Aviv et al. 2016 Review[12]	1990-2015	• Preliminary studies suggest treatment with cannabinoids may decrease PTSD symptoms including sleep quality, frequency of nightmares, and hyperarousal. • No large scale, randomised controlled studies investigating this specifically.

3.3 Nausea and Vomiting

Evidence used by WSV at time of writing of this report (Table 4) concluded that there is evidence that synthetic THC is effective in reducing chemotherapy-induced nausea and vomiting, but antiemetics that are not currently in use were compared, limiting our understanding of its current therapeutic use.[2, 5, 14, 15]

Table 4. *Summary - Medicinal Cannabis and Nausea/Vomiting*

Level I or II Evidence	Timeframe	Key outcomes/recommendations
NASEM 2017 cannabis evidence review,[5] Whiting SR 2015,[7] Smith Cochrane 2015,[14] RACGP Cannabis position statement 2019[2]	1999-2016	• Synthetic THC (not cannabidiol) is effective for chemotherapy-induced nausea and stimulated appetite in AIDS patients. • Nausea is a side effect of cannabis use and a symptom of cannabis withdrawal syndrome (which is mild and short-lived). • RACGP found very low-quality evidence for the treatment of chemo-nausea; noted the side effect of nausea. • No research was identified for other causes of nausea (i.e., gastroparesis or opiate-induced).

4. CHRONIC PAIN FINDINGS

4.1 Introduction

A systematic review found that pain was the most common reason for medicinal cannabis use (67%),[16] and pain management was noted as one of the major areas of focus in relation to medicinal cannabis studies (Figure 1).[19]

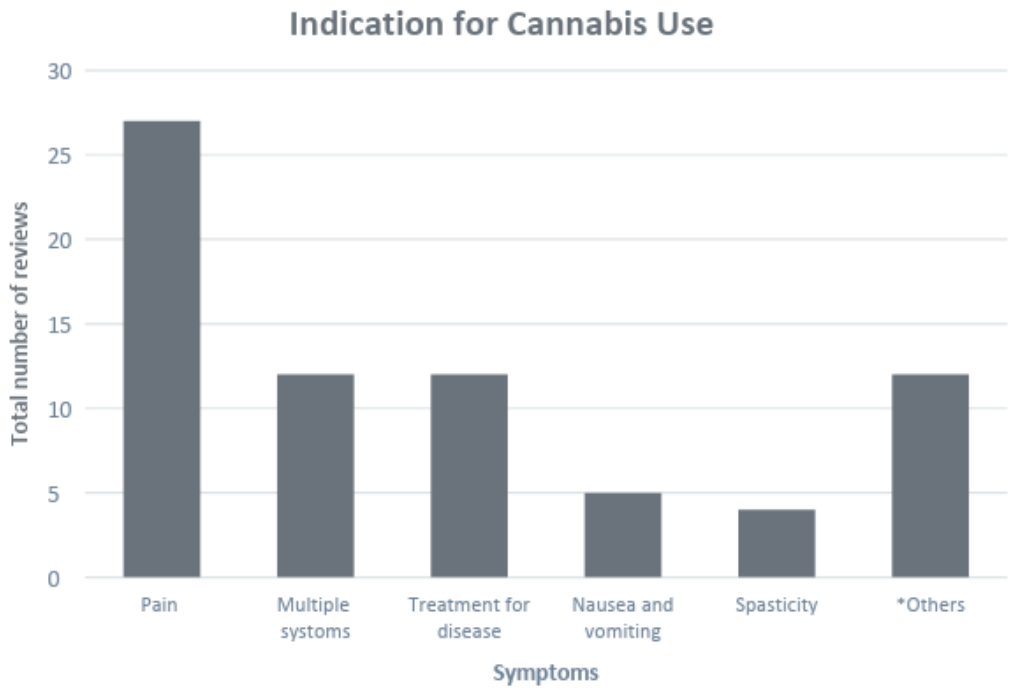

Fig 1. Indication for cannabis use adapted from Pratt et al. 2019[19]

**Others: include Mental health and behaviour (3); Bladder control (2); Anorexia and weight (2); Sleep problems (1); Morbidity and mortality (1); Gait problems (1); Ataxia (1) and Muscle cramps (1).*

4.2 Key findings

Two systematic reviews of systematic reviews and four other systematic reviews were identified (see Table 5). As per the evidence reviewed, different types of chronic pain were distinguished (including nociceptive, orthopaedic and neuropathic pain), and it is recognised that there is considerable overlap.

Results indicated that, compared to placebo, medicinal cannabis may be effective (Level I evidence) for reducing general chronic pain and nociceptive pain, as well as orthopaedic pain (Level IV evidence). Evidence to support the efficacy of medicinal cannabis for neuropathic pain is discordant (Level I evidence). There was no evidence for its effectiveness in headaches/migraines. The therapeutic potential of medicinal cannabis for chronic pain was limited by its efficacy (marginal decreases in pain compared to placebo in low numbers of participants), by its frequently reported mild harms, and an increased risk for serious adverse events.

1. Medicinal cannabis may be effective in reducing chronic pain

- There is Level I systematic review evidence[24] which indicated that medicinal cannabis may be effective in reducing chronic pain compared to placebo. This systematic review of systematic reviews found two Level I systematic reviews that looked at medicinal cannabis for any type of

chronic pain, and neither performed subgroup analyses of cannabis-based medicines and dosages. Martin-Sanchez et al. (2009) stated that cannabis treatment is moderately efficacious for treatment of chronic pain, but beneficial effects may be partially (or completely) offset by potentially serious harms. Whiting et al. (2015) concluded that there was moderate quality evidence to support the use of cannabis-based medicines for the treatment of chronic pain.

- There were inconsistent results on tolerability and safety of cannabis-based medicines for any chronic pain[24]; adverse effects such as elevated risk for euphoria and number needed to harm (NNTH) were noted.
- The majority of studies in both systematic reviews were determined to have a high risk of bias, despite being RCTs.[24]

2. There is mixed/inconsistent evidence that medicinal cannabis reduces chronic neuropathic pain

- Estimates of the population prevalence of chronic pain with neuropathic components ranged between 6% and 10%.[27] Neuropathic pain is pain coming from damaged nerves as opposed to pain messages that are carried along healthy nerves from damaged tissue.
- Of the five systematic reviews with Level I evidence, three[22, 27, 28] found medicinal cannabinoids may be effective for reducing chronic neuropathic pain compared to placebo, and two[24, 25] found inconsistent findings on the efficacy of cannabis-based medicines in neuropathic pain compared to placebo.
- Where indicated as effective relative to placebo, reductions in pain of ≥30% to ≥50% were achieved by small numbers of patients. For example, Mucke's Cochrane review of 10 RCTs (Level I evidence) indicates that cannabis-based medicines probably increases the number of people obtaining ≥30% reduction in pain: 39% (medicinal cannabis) versus 33% (placebo) (risk difference (RD = 0.09, 95% CI: 0.03 to 0.15).[27]
- One systematic review (Level I) specified that cannabis preparations with precisely defined THC:CBD content (most in a 1:1 or 2:1 ratio) had the potential to reduce neuropathic pain, but insufficient evidence in other patient populations.[25] The applicability of these findings to current practice may be low in part because the formulations studied may not be reflective of what most patients are using.
- It is possible that the harms of cannabis-based medicines may outweigh the benefits.[24, 27, 29]
- Even for the Level I systematic reviews, the evidence was considered low/insufficient in most studies; studies were small; many had methodological flaws; and the long-term effects were unclear given the brief follow-up of most studies.[22, 25, 27, 28]

3. Medicinal cannabis may be effective in reducing orthopaedic pain

- One systematic review[26] (Level IV evidence) found that most of the existing evidence suggests that medicinal cannabis is effective for orthopaedic pain relative to placebo or when there is no comparator. Studies using an active comparator did not demonstrate efficacy. Study quality was generally low to moderate.
- Studies using higher doses tended to conclude that cannabis use was effective, but the potential for harmful effects may also be increased with higher doses.[26]

4. Medicinal cannabis may be effective in reducing nociceptive pain

- One systematic review [28] (Level I) was identified in relation to nociceptive pain.
- The administration route and type of formulation affected reduction in nociceptive pain: Standardised Cannabis Extract with THC (SCET) via the oral route was found to reduce nociceptive pain relative to placebo.[28]
- The evidence was limited to few studies, thus making it difficult to draw firm conclusions.

5. No evidence that medicinal cannabis is effective for reducing headaches/migraines

- No systematic reviews were identified for medicinal cannabis in relation to headaches/migraines.
- While there might be some plausible mechanisms, and many clinicians in the United States are prescribing medicinal cannabis for the treatment of migraines and headaches (and patients self-report therapeutic benefits), there were no systematic reviews for the use of cannabis in headache disorders (e.g., migraines, tension headaches, and cluster headaches).[31]
- One exception: Lochte et al. (2017) in their brief review identified only one clinical trial of a synthetic cannabinoid (nabilone) which showed efficacy for medication overuse headache (a chronic condition which develops from frequent use of anti-headache medications).[31]

4.3 Additional limitations

Complexity of chronic pain. A shortcoming noted in many of the systematic reviews examining chronic pain was that they combined different types of chronic pain in one review, and that there is a lack of differentiation for the complex presentation of chronic pain, also echoed in the FPM 2019 Statement.[20] Häuser, Finnerup and Moore (2018) in their commentary on systematic reviews of cannabis medicines for chronic pain, note that: "Lumping all chronic pain syndromes together does not help in managing individual patients, given the heterogeneity of chronic pain and its mechanisms. Even the importance of subgroup analyses is limited: cancer pain might have nociceptive and/or neuropathic components; neuropathic pain can have many dimensions, and drugs might be effective for some dimensions of neuropathic pain but not for others".[21]

Mild harms were frequently reported which limit the usefulness of medicinal cannabis for chronic pain (e.g., alterations to perception, euphoria).[19] More participants withdrew from studies due to adverse events: cannabis-based medicines (10%) vs. placebo (5%) (e.g., due to sleepiness, dizziness, confusion).[27] Cannabis-based medicines may also increase nervous system adverse events compared with placebo (61% versus 29%).[27] Psychiatric disorders occurred in 17% of participants using cannabis-based medicines and in 5% using placebo.[27]

Route, dosage, standardisation of formulations. The Rabgay et al. 2020 systematic review (25 studies involving 2,270 patients) and meta-analysis found that administration routes had an effect on reducing different types of pain: for nociceptive pain only standardised cannabis extract via oral route reduced pain score; neuropathic pain scores improved with THC/CBD oromucosal route or dried cannabis via inhalation route.[28] It is also noted that it was difficult to compare doses across studies as there is a lack of standardisation of formulations and pharmacokinetic activity (e.g., variances in bioavailability between oral sprays and oral capsules).[32]

4.4 Opioid-sparing effect

Examination of the opioid-sparing effect of medicinal cannabis was not within the scope of this project and so specific papers addressing this were not included in the search. However, several references reviewed as part of this research discussed aspects of this topic. More than 35% of people using cannabis for medicinal purposes self-reported use as a substitute for opioids/narcotics to treat pain.[17] A four-year prospective cohort study in which 20% of people were using cannabis for pain, found it did not produce an opioid-sparing effect.[10] There is pre-clinical evidence from a recent review that cannabinoids may produce an opioid-sparing effect (thus reducing opioid dependence/abuse).[18] This review also looked at synergistic effects when opioids and cannabinoids were co-administered: in pre-clinical work, where less opioids were needed if cannabinoids were co-administered - doses of morphine and codeine required to produce the same analgesic effect were 3.6 and 9.5 times lower, respectively,

when co-administered with delta-9-THC. However, this has not been evidenced in clinical studies, with the authors noting that no randomised controlled studies were identified that provided evidence of an opioid-sparing effect of cannabinoids.

4.5 Limitations and Conclusion – chronic pain

This review of medicinal cannabis pointed to its potential efficacy (Level I evidence) in reducing general chronic and nociceptive pain, as well as orthopaedic pain (Level IV evidence). Evidence around the effectiveness of medicinal cannabis for neuropathic pain (Level I evidence) was mixed. The evidence in the systematic reviews was limited by low quality data, in addition to a risk of bias in the studies, a lack of standardisation in formulations, dosages and administration routes across studies, and a lack of longitudinal research on long-term outcomes. No evidence was identified for reducing migraines/headaches. The therapeutic potential of medicinal cannabis for pain was limited by its frequently reported mild harms, and an increased risk for serious adverse events.

Table 5. *Key characteristics and findings of Systematic Reviews - Chronic Pain*

Reference, Year (Country)	No. of Databases (Years searched)	No. of Primary Studies (NHMRC Level of Evidence)	Intervention (control) (participants)	Population of Interest	Key Outcomes	Key Findings	SR Authors' Quality Ratings/Comments
Allan 2018[22] (Canada)	2 (Any date to May 2017)	31 SRs of RCTs (15 RCTs in meta-analysis; 87% on neuropathic pain) **(Level I)**	Medicinal cannabinoid (placebo) (*N* = 1,985)	Patients with predominantly chronic neuropathic pain	**≥30% reduction in pain. Response:** 39% of patients taking medicinal cannabis attained ≥30% ↓in pain, compared with 30% of placebo patients (RR =1.37; 95%CI: 1.14 to 1.64)	There is some uncertainty about whether cannabinoids improve pain, but if they do, it is neuropathic pain and the benefit is likely small. **Adverse events** are very common, meaning benefits would need to be considerable to warrant trials of therapy.	Authors' GRADE rating: Overall, very low owing to serious risk of bias, serious inconsistency, serious indirectness, and serious imprecision.
Häuser 2018[24] (Germany)	3 (January 2009 - January 2017)	10 SRs of RCTs **(Level I)**	Cannabis medicines (placebo/ active comparator)	Patients with chronic pain (general)	**Reduction in pain. Response: Two SR's focused on chronic pain (38 studies):** Martin-Sanchez et al. (2009)[33] found cannabis treatment is moderately efficacious for treatment of chronic pain, but beneficial effects may be offset by potentially serious harms. Whiting et al. (2015)[7] concluded that there was moderate quality evidence to support cannabis-based medicines for the treatment of chronic pain.	There are inconsistent results on tolerability and safety of cannabis-based medicines for any chronic pain.	AMSTAR# quality rating: Methodological quality high in four SR and moderate in six of the SR. The majority of the studies included in the noted SR's[7, 33] had a high risk of bias.
				Patients with chronic neuropathic pain	There were **inconsistent findings** in four SRs on the efficacy of cannabis-based medicines compared to placebo for chronic **neuropathic pain**.		

Reference, Year (Country)	No. of Databases (Years searched)	No. of Primary Studies (NHMRC Level of Evidence)	Intervention (control) (participants)	Population of Interest	Key Outcomes	Key Findings	SR Authors' Quality Ratings/Comments
Kansagara 2017[25] (US) Linked to Nugent et al. 2017[9] – which is reviewed in Allan et al. 2018[9]	6 (Any date to February 2016)	60 (13 RCTs on neuropathic pain, 9 RCTs in meta-analysis) **(Level I)**	Cannabis (whole plant/ extracts such as Nabixmols and THC/ CBD capsules (excluded synthetics, e.g., dronabinol or nabilone) (*N* = 593)	Patients with chronic neuropathic pain	**≥30% reduction in neuropathic pain Response:** Meta-analysis of 9 RCTs: ≥30% ↓neuropathic pain more likely in intervention groups (combined RR, 1.43 [95% CI: 1.16 to 1.88]; I^2 = 38.6%; p = 0.111).	Found low-strength evidence that cannabis preparations with precisely defined THC:CBD content (most in a 1:1 to 2:1 ratio) have the potential to improve neuropathic pain, but insufficient evidence in other patient populations.	Authors noted evidence was low / insufficient in most studies; studies were small; methodological flaws in many; long-term effects were unclear given brief follow-up of most studies. **Limitations:** Marked differences in dosing and delivery. Most studies were small, few reported outcomes beyond 2 to 3 weeks, and none reported long-term outcomes.
Madden 2019[26] (Canada)	4 (Any date to 1 May 2017)	33 (12 SRs which included 9 RCTs, and 21 primary studies including 5 RCTs) **(Level IV)**	Cannabis (placebo/ active comparator) (*N* = 5,310)	Patients with orthopaedic pain (post-trauma, post-surgery, back, arthritis)	**Orthopaedic pain:** Most of the existing evidence suggests that medical cannabis use is effective, but this efficacy has been demonstrated only when either there is no comparator or cannabis is compared with placebo. Studies using an active comparator have not demonstrated efficacy. Studies using higher doses tended to conclude that cannabis use was effective.	Variability in the methodologies of cannabis research makes it difficult to gain insights about dosing, routes and frequency of administration. The potential for harmful effects may also be increased with higher doses.	Authors noted minimal high-quality evidence for efficacy of medical cannabis in pain management for core orthopaedic areas of arthritis pain, post-surgical pain, back pain and post-trauma pain.
Mücke 2018[27] (Germany)	3 (Any date to November 2017)	16 RCTs **(Level I)**	Cannabis-based medicines (plant-derived THC and CBD combination, nabilone, inhaled	Patients with chronic neuropathic pain	**May increase number of people obtaining ≥50% reduction in pain** (indicated as *worthwhile pain relief*): ↓pain 21% (cannabis) vs 17% (placebo) (risk difference (RD) 0.05, 95% CI: 0.00 to 0.09).	All cannabis-based medicines pooled together were better than placebo for reducing pain intensity, sleep problems and psychological distress.	The authors commented that there was limited high quality evidence in studies analysed: Study quality was low in two studies, moderate in 12 studies and high in two studies. Nine

Reference, Year (Country)	No. of Databases (Years searched)	No. of Primary Studies (NHMRC Level of Evidence)	Intervention (control) (participants)	Population of Interest	Key Outcomes	Key Findings	SR Authors' Quality Ratings/Comments
			herbal cannabis, dronabinol) (Mostly placebo and one study analgesic – dihydrocodeine) (*N* = 1,750)		**Probably increases the number of people obtaining ≥30% pain reduction:** ↓pain 39% (cannabis) versus 33% (placebo) (RD 0.09, 95% CI: 0.03 to 0.15). Studies ranged from 2-26 weeks. The authors found no information about long-term risks in the studies analysed.	Evidence was very low- to moderate in quality. **Adverse events:** More participants withdrew from the studies due to adverse events: cannabis-based medicines (10%) vs. placebo (5%) (sleepiness, dizziness, confusion). ↑Nervous system adverse events (cannabis 61% vs. placebo, 29%). Psychiatric disorders 17% cannabis vs. 5% placebo.	studies were at high risk of bias for study size. They rated the quality of the evidence according to GRADE* as very low to moderate. Potential benefits of cannabis-based medicines might be outweighed by the potential harms.
Rabgay 2020[28] (Thailand)	6 (Any date to June 2017)	25 RCTs **(Level I)**	Cannabis/ Cannabinoids – excluding synthetics (mostly placebo; 3 with anxioloytics - diazepam) (*N* = 2,270)	Patients with pain	**Visual analogue scale/numeric rating scale. Response:** In order of effectiveness, (compared to placebo), Standardised Cannabis with THC (SCT) via inhalation ↓neuropathic pain (most effective), then THC via oromucosal route ↓neuropathic pain, and then THC/CBD via oromucosal route for ↓neuropathic pain. Compared to placebo, Standardised Cannabis Extract with THC (SCET) via oral route could ↓nociceptive pain (but not THC via oral route).	Administration route of different formulations had different effects on different types of pain, with standardised cannabis with THC via inhalation most effective for neuropathic pain. **Adverse events:** (focused on euphoria) THC/CBD via oromucosal route and THC via oromucosal route ↑euphoria vs. placebo in neuropathic pain patients when mean dose was 22.96mg/day.	Authors' quality assessment noted that most studies included had a low risk of bias, but a few lacked randomisation (high risk of bias).

[#]AMSTAR = assessment of the methodological quality of systematic reviews; *GRADE - Grading of recommendations Assessment, Development and Evaluating; SR = Systematic Reviews; RCT(s) = Randomised controlled trials; RR = Risk Ratio; CI = Confidence Interval; SMD = Standardised Mean Difference

5. MENTAL HEALTH FINDINGS

5.1 Introduction

Self-reported patient data indicated that medicinal cannabis was frequently used for mental health problems. A meta-analysis (data from 13 studies, 6,665 participants, 30 countries) found that anxiety was the reason for medicinal cannabis use in 52% of participants, and depression in 35%.[16] This is an emerging area of research, and research examining the effect of cannabinoids on mood and anxiety disorders were much less common than the effects of cannabinoids on psychoses (studied more widely).[36]

5.2 Key findings

Ten systematic reviews (four Level I and six Level IV) were identified (see Table 6). Results show that medicinal cannabis may be effective in improving symptoms of social anxiety disorder (Level I and IV evidence). However, there was mixed/inconsistent evidence that medicinal cannabis was effective for anxiety disorder in general (Level I evidence) and for post-traumatic stress disorder (Level I and IV evidence). Medicinal cannabis had no therapeutic effect on the symptoms of depression (Level I evidence) and bipolar disorder (Level IV evidence), with some indication that it might worsen symptoms in both these indications. No effect for remission of any mental health disorders was noted. Adverse events, side effects and low-quality evidence (e.g., few RCTs) limits certainty of safety and efficacy, in what is an emerging field of research.

1. There is mixed/inconsistent evidence that medicinal cannabis is effective for (general) anxiety disorders
   - There was Level I evidence that pharmaceutical THC (with or without CBD) leads to a small improvement in symptoms of anxiety among individuals with other medical conditions (e.g., Chronic Non-Cancer Pain and Multiple Sclerosis).[37]
   - One systematic review (Level I) examining nabilone for generalised anxiety disorder was inconclusive (variable results showing improvement in one RCT, but not in another).[41]
   - While limited positive findings were identified, the quality of the evidence was low due to small sample sizes, high risk of bias, and methodological issues.

2. Medicinal cannabis may be effective for social anxiety disorders
   - Six systematic reviews (three Level I[38, 40, 41] and three Level IV[36, 43, 44] - mostly citing the same two small RCTs - *Bergamaschi et al. (2011) (N* = 36*)* & *Crippa et al. (2011) (N* = 10*)* reported that medicinal cannabis was effective in reducing social anxiety disorder symptoms (e.g., public speaking fear, performance-related anxiety onset, comfort in speech performance).
   - It should be noted that effect estimates tend to be larger in studies with small sample sizes and as such, caution should be taken when interpreting outcomes based on studies with small sample sizes.[6]
   - Data were very limited to a small number of positive studies.

3. There is mixed/inconsistent evidence that medicinal cannabis is effective for Post-Traumatic Stress Disorder (PTSD)

- Seven systematic reviews (three Level I[37, 40, 41], four Level IV[36, 42, 43, 44]) most citing the same small RCT (*Jetley et al. 2015* – see comment above relating to small RCTs) found that medicinal cannabis may be effective in reducing some symptoms of PTSD, however the data were limited to low quality studies, including clinical case-studies. Three ongoing trials were identified.[38]
- In terms of specific symptom improvement, most of the cited systematic reviews agreed that medicinal cannabis was effective in improving global functioning (clinician-rated), and decreasing both nightmare frequency and sleep disturbances. Decreases in hyperarousal and anxiety were reported in some reviews. Improvements in sleep quality were noted in some reviews, but others found no effect on sleep quality for PTSD patients.
- Specifically, Nabilone (*Jetly et al.* 2015 RCT) might be beneficial in treating nightmares and sleep in PTSD, but there were notable adverse event rates.[36, 37, 39, 40, 41]
- Very few RCTs have been conducted, and two Level IV systematic reviews (Kansagara et al. 2017[25] and Hindocha et al. 2020[39]) found insufficient evidence to conclude that cannabis improved outcomes for patients with PTSD, noting that "the clinical effectiveness for PTSD remains largely hypothetical".[39]

4. Medicinal cannabis is not effective for depression and may worsen symptoms

- Two systematic reviews (Level I) reported that medicinal cannabis was not effective in reducing depressive symptoms.[37, 38].
- Higher doses of THC in chronic pain patients with depression were associated with an increase in depressive symptoms (Level IV evidence).[43]
- A longitudinal population-based study indicated that prolonged cannabis use (after 3 years) was associated with increased depressive symptoms (Level IV evidence).[36]
- There was a lack of RCTs focused on cannabinoids as treatment for depression.[36, 44]
- From the available evidence, it appears not only unlikely to have any therapeutic benefit, but could worsen symptoms, with some authors concluding that it is contraindicated for major depressive disorder.[43]

5. Medicinal cannabis is not effective for bipolar disorder and may worsen symptoms

- One systematic review (Level IV) identified that cannabis did not decrease bipolar patients' mania,[43] with another systematic review (Level IV) showing increases in severity, persistence and frequency of manic episodes, and increases in psychotic features.[36]
- There was scant information available on whether medicinal cannabis was effective for bipolar disorder. From the available evidence it is not only unlikely to have any therapeutic benefit, but may worsen symptoms, with some authors concluding that it is contraindicated for bipolar disorder.[36]

5.3 Limitations and Conclusion – mental health

The findings indicate that while medicinal cannabis may have an effect on mental health symptoms, it was not associated with remission of any mental health disorders.[40] The use of medicinal cannabis for mental health indications is an emerging area, characterised by limited evidence, and a lack of rigorous clinical trials. [38, 42, 43] There is currently minimal evidence regarding the safety and efficacy of medicinal cannabis for the treatment of all mental health problems.[38]

The majority of systematic reviews supplemented their limited RCT data with longitudinal cohort studies, cross-sectional studies and clinical case studies (i.e., lower levels of evidence).[36, 39, 43, 44] In terms

of quality and the weight of evidence, the studies reviewed in these systematic reviews had small sample sizes, focused on short term outcomes, the methodological quality was low with a high risk of bias, and there was heterogeneity of findings across studies.[36, 37, 44] Reported improvements were mostly assessed in single RCT's with small sample sizes: many of the systematic reviews cited the same small RCTs (e.g., in social anxiety disorder and PTSD), and these results should not be interpreted as compounding the body of evidence. As noted above, small RCTs tend to overestimate effect estimates,[6] thus further limiting confidence in these findings.

As with the chronic pain evidence reviewed, the systematic reviews on medicinal cannabis referred to variable administration routes, variable dosages and different types of cannabinoids studied, limiting an understanding of its therapeutic potential.[42] The systematic reviews also often included populations where the main study outcome/population was not mental health (e.g., patients with chronic pain in which mental health was also studied as a secondary outcome).[37] Treatment users are also often not naïve to cannabis, or presented with comorbidities. For example, Orsolini et al. (2019) found that there was a significant overlap between substance use disorder and PTSD (patients with PTSD were 2-4 times more likely to have substance use disorder, compared to those without PTSD).[42]

Thus, the conclusions are limited by a lack of well controlled studies that are specifically applied to clinical populations.[36] Like others expressing low confidence in the evidence to make reliable treatment recommendations for use in routine clinical practice,[25, 36, 39-41, 43, 44, 47] the Black et al. (2019) systematic review (funded by TGA, Commonwealth Department of Health, NHMRC and NIH) published in The Lancet concluded that there remains insufficient evidence to provide guidance on the use of cannabinoids for treating mental disorders within a regulatory framework.[37]

Table 6. *Key characteristics and findings of Systematic Reviews - Mental Health*

Reference, Year (Country)	No. of Databases (Years searched)	No. of Primary Studies (NHMRC Level of Evidence)	Intervention (control)	Population of Interest	Key Outcomes	Key Findings	SR Authors' Quality Ratings/Comments
Black 2019[37] (Australia)	5 (1 January 1980 – 30 April 2018)	83 studies (meta-analysis: 7 RCTs for anxiety; 12 RCTs for depression, 10 RCTs in adverse events) **(Level I)**	Medicinal cannabinoids (pharmaceutical THC-CBD) (placebo, other types of active treatments)	Adults with depression, anxiety, PTSD	**Anxiety symptoms. Response:** Pharmaceutical THC (with/without CBD) ↓ anxiety symptoms (small effect) among individuals with other medical conditions (CNCP and Multiple Sclerosis) (SMD = 0.25 (95% CI: -0.49 to -0.01), (7 RCTs in meta-analysis, *N* = 252). **Depressive symptoms. Response:** None studied in populations where depression was primary (e.g., chronic pain patients). Pharmaceutical THC-CBD - no change in depressive symptoms compared to placebo (SMD =-0.05 (95% CI: -0.20 to 0.11), 12 RCTs in meta-analysis, *N* = 1,656). **PTSD symptoms. Response:** Identified only 1 RCT (*Jetly et al. 2015*, *N* = 10) found pharmaceutical THC-CBD (Nabilone) had significant ↑global functioning and ↓nightmare frequency compared to placebo. No effect on sleep quality.	Scarce evidence to suggest that cannabinoids improved depressive disorders and symptoms, anxiety disorders, post-traumatic stress disorder. **Adverse events:** Across mental health conditions pharmaceutical THC-CBD = significantly more adverse events compared to placebo (OR = 1.99 (95% CI: 1.2 to 3.29) (10 RCTs, *N*=1,495)	Authors' GRADE[#] rating: Low or Very Low. Authors concluded that there was insufficient evidence to provide guidance on the use of cannabinoids for treating mental disorders within a regulatory framework. **Limitations:** Small amount of available data, small study sizes, and heterogeneity of findings across studies.
Bonaccorso 2019[38] (UK/Italy)	3 (Any date to 31 January 2019)	27 RCTs **(Level I)**	Cannabidiol (placebo)	Patients with social anxiety disorders	**Social anxiety symptoms. Response:** Compared to placebo ↓significantly decreased anxiety scores & ↓significantly inhibited the fear of speaking in public (only 2 RCTs	The available trials reported potential therapeutic effects for specific psychopathological conditions, such as anxiety.	Authors noted that further large scale RCTs are required to better evaluate efficacy of CBD in both acute and chronic illnesses,

Reference, Year (Country)	No. of Databases (Years searched)	No. of Primary Studies (NHMRC Level of Evidence)	Intervention (control)	Population of Interest	Key Outcomes	Key Findings	SR Authors' Quality Ratings/Comments
					identified, *Bergamaschi et al. (2011) (N* = 36*)* & *Crippa et al. (2011) (N* = 10)	But, the overall interpretation on the role of cannabidiol in psychiatric disorders is far from clear. **Side effects:** The only side effects noted in these studies were sedation (but the authors note further studies are needed to assess its impact on: suicidal ideation, risk of gastrointestinal events, liver function, drug interactions).	as well as any possible abuse liability. No RCTs evaluating the efficacy of cannabidiol in reducing symptoms of PTSD have been completed, but 3 ongoing trials were identified.
				Patients with other mental health disorders	**Symptoms of other mental health disorders** (i.e., mood, neurocognitive, sleep, personality, eating disorders, obsessive compulsive disorders, trauma stress, dissociative and somatic disorders)**. Response:** Inconclusive or weak data.		
Botsford 2020[36] (Canada)	1 (January 1990 - May 2018)	47 (longitudinal cohort, RCTs, cross-sectional) **(Level IV)**	Cannabis use and cannabinoid treatment as active intervention	Patients with depression	**Depressive symptoms. Response:** A longitudinal population-based study found that cannabis use is associated with ↑depression symptoms after 3 years. No studies meeting criteria were identified as cannabinoid therapeutics for depression.	There is therapeutic potential of cannabinoids in PTSD and anxiety disorders (remission rates and reduced social anxiety symptoms). No therapeutic benefit identified for depression and bipolar disorder, and looks likely to worsen symptoms. Co-morbid substance use and/or substance use disorders, as well as psychosocial factors mediate and/or confound the relationship between cannabis and mental health.	Authors noted that conclusions were limited by a lack of well-controlled longitudinal studies specifically applied to clinical populations.
				Patients with bipolar disorder	**Bipolar disorder. Response:** Cannabis negatively affect multiple disease measure of bipolar disorder: ↑severity, ↑persistence and ↑frequency of manic episodes and ↑psychotic features. Very scant information is available on cannabinoid as therapeutic in bipolar disorder.		
				Patients with social	**Social anxiety symptoms. Response:** Cannabinoid ↓public speaking fear in		

Reference, Year (Country)	No. of Databases (Years searched)	No. of Primary Studies (NHMRC Level of Evidence)	Intervention (control)	Population of Interest	Key Outcomes	Key Findings	SR Authors' Quality Ratings/Comments
				anxiety disorder	students with social anxiety disorder (1 RCT identified, *Bergamaschi et al. (2011)* (*N* = 36)	**Adverse events:** Notable adverse event rates in for Nabilone where used in two studies for PTSD (9.6% and 28%).	
				Patients with PTSD	**PTSD symptoms. Response:** One RCT (*Jetly et al. 2015*) with nabilone (*N* = 10) compared with placebo beneficial in ↓nightmares and ↑sleep associated with PTSD.		
Hindocha 2020[39] (UK)	3 (Any date to 15 December 2018)	10 (1 RCT, 3 open label trials/pilots; observational, cases studies) **(Level IV)**	Medicinal cannabinoids (nabilone, THC, CBD, whole plant products – herbal and resin)	Patients with PTSD	**PTSD symptoms. Response:** The clinical effectiveness of cannabinoids for the treatment of PTSD remains largely hypothetical. Cannabinoids may ↓PTSD symptomology (i.e., sleep disturbances and nightmares), although quality of studies low. (Also cites *Jetly et al. 2015*)	There is insufficient and poor quality evidence of the effectiveness of cannabinoids for PTSD. **Adverse effects:** may cause severe side effects in people with a history of psychosis, and mild to moderate effects included dry mouth, feeling "stoned," and stomach irritations.	Only low levels of evidence exist. Available studies were small and had a high risk of bias, thus precluding any clinical recommendations about its use in routine clinical application for PTSD. **Limitations:** Authors cautioned that studies were small and of low quality (high risk of bias).
Hoch 2019[40] (Germany)	5 (2006 – August 2018)	18 (1 RCT social anxiety disorder; 1 RCT PTSD) **(Level I for social anxiety and PTSD. Remainder of studies not included in our review)**	Medical cannabis (placebo; and other medication (e.g., benzodiazepines) and psychotherapy were available in most studies)	Patients with social anxiety disorder	**Social anxiety symptoms. Response:** *(cites Bergamaschi et al. (2011)* Indicative of ↓performance-related anxiety onset in group receiving cannabidiol compared to placebo (1 RCT, *N* = 36)	THC- and CBD-based medicines were associated with improvements of several symptoms of mental disorders, but not with remission. Reported improvements were mostly assessed in single RCT's with small sample sizes. **Adverse events:** Side effects can occur, but Severe Adverse	Overall low confidence in the evidence, and reliable treatment recommendations could not be made.
				Patients with PTSD	**PTSD symptoms. Response:** One RCT (*Jetly et al. 2015*) with Nabilone (*N* = 10) compared with placebo showed significant ↓nightmares; no improvement in sleep intensity/quality;		

Reference, Year (Country)	No. of Databases (Years searched)	No. of Primary Studies (NHMRC Level of Evidence)	Intervention (control)	Population of Interest	Key Outcomes	Key Findings	SR Authors' Quality Ratings/Comments
					↑global improvement in symptoms (clinician rated).	Events were only mentioned in single cases.	
Kansagara 2017[25] (US)	6 (up to February 2016)	60 (PTSD 2 observational studies) **(Level IV)**	Cannabis (whole plant/ extracts such as Nabixmols and THC/ CBD capsules (excluded synthetics e.g., Dronabinol or Nabilone)	Patients with PTSD (*N* = 2,976)	**PTSD symptoms. Response:** Two observational studies comparing outcomes in cannabis users to a control group that had not used cannabis; cannabis use not associated with improved outcomes.	Found insufficient evidence examining the effects of cannabis in patients with PTSD.	Evidence is low or insufficient in most studies, studies were small, many had methodological flaws, and the long-term effects were unclear given the brief follow-up of most studies.
Lim 2017[41] (Singapore)	3 (Any date to April 2017)	24 RCTs **(Level I)**	Any form of cannabis (placebo, usual care, active treatments)	Patients with anxiety	**Anxiety (and social anxiety) symptoms. Response:** 5 RCTs (*N* = 82), including 2 RCTs on social anxiety *Bergamaschi et al. (2011) and Crippa et al. (2011).* Two Nabilone trials showed variable results for generalised anxiety (one showed significant improvement, but the other not). Social anxiety ↓ symptoms with cannabinoids compared to placebo groups. Also, indicative ↓performance-related anxiety onset *(same as Bonaccorso 2019 above).*	While some trials with positive findings were identified in anxiety disorders and in PTSD, definitive conclusions on the efficacy of medical cannabis cannot be drawn due to small sample sizes, high risk of bias and methodological issues. **Adverse effects:** Cannabinoids appear to be well-tolerated in these trials. The common short-term effects included dry mouth, dizziness, tiredness, and headache.	Evaluation of these low-quality trials, as rated on the Cochrane risk of bias tools, made difficult by methodological issues (e.g., inadequate description of allocation concealment, blinding and underpowered sample size). Authors noted that more adequately powered controlled trials examining long- and short-term efficacy, safety and tolerability, and mechanisms underpinning
				Patients with PTSD	**PTSD symptoms. Response:** *Same as Hoch 2019 above citing Jetly et al. 2015 RCT (N = 10).*		

Reference, Year (Country)	No. of Databases (Years searched)	No. of Primary Studies (NHMRC Level of Evidence)	Intervention (control)	Population of Interest	Key Outcomes	Key Findings	SR Authors' Quality Ratings/Comments
							therapeutic potential, were warranted.
Orsolini 2019[42] (Italy)	4 (Any date to 31 May 2019)	12 studies (observational studies, case-control studies and 1 RCT) **(Level IV)**	Cannabis/ synthetic cannabinoid (some with placebo)	Patients with PTSD	**PTSD symptoms. Response:** Present data show that cannabis and synthetic cannabinoids, both acting on the endocannabinoids system, may have a potential therapeutic use for improving PTSD symptoms, e.g., reducing anxiety, modulating memory-related processes, and improving sleep. *(also cites Jetly et al. 2015).*	While current literature suggested that cannabis/ synthetic cannabinoids may play role in treatment of PTSD, there was limited evidence regarding its safety and efficacy. **Adverse effects:** headache, dizziness, dry mouth. Abrupt discontinuation of daily synthetic cannabinoid can 3-4 days later precipitate mood swings, and physical symptoms such as weakness, sweating, restlessness, dysphoria, sleeping problems, anxiety, craving.	Authors noted that evidence was limited by few RCTs, small heterogenous sample features, pre-treatment cannabis users; concomitant substance use; variable administration route, variable dosage and different types of cannabinoids. **Limitations:** Extreme heterogeneity of methodological strategies.
Sarris 2020[43] (Australia)	5 (Any date to July 2019)	13 clinical studies (included RCTs and observational studies) **(Level IV)**	Cannabis (whole plant) medicines, cannabis derived isolates (not synthetics) (placebo)	Patients with social anxiety disorder	**Social anxiety symptoms. Response:** 2 RCTs (same as noted above - *Bergamaschi et al. (2011) (N* = 36*)* & *Crippa et al. (2011) (N* = 10*)***.** Cannabidiol significantly ↓lower subjective social anxiety and ↓discomfort in speech performance compared to placebo.	Isolated positive studies have, revealed tentative support for cannabidiol for reducing social anxiety. Case studies suggest that medicinal cannabis may be beneficial for improving sleep and post-traumatic stress disorder,	Evidence was limited by low number of RCTs to draw on; emerging area of research. There was limited evidence for medicinal cannabis in the treatment of a range of psychiatric disorders.
				Patients with PTSD	**PTSD symptoms. Response:** (2 retrospective studies): (*N* = 80, cannabis – not defined) >75% in ↓clinician		

Reference, Year (Country)	No. of Databases (Years searched)	No. of Primary Studies (NHMRC Level of Evidence)	Intervention (control)	Population of Interest	Key Outcomes	Key Findings	SR Authors' Quality Ratings/Comments
					assessed PTSD scores; (*N*=11) 28% reduction in symptoms with cannabidiol (on PCL-5 which measures DSM-V PTSD symptoms) (↓anxiety; ↑sleep).	however evidence is currently weak. Generally favourable safety profile. Clinicians need to be mindful of a range of other prescribed medicines and occupational safety considerations, especially if initiating higher dose THC formulations (avoidance in people with major depressive disorder, and psychotic disorders). Thought should be given to gradual titration, regular assessment, and caution in cardiovascular and respiratory disorders, pregnancy and breastfeeding.	
				Patients with depression	**Depression symptoms. Response** (1 RCT of chronic pain patients, *N* =263: Higher doses of THC (Nabiximol) ↑depressive symptoms.		
				Patients with bipolar disorder	**Bipolar symptoms. Response** (no trials, 1 case study *N* = 2): Not effective in ↓mania.		
Walsh 2017[44] (Canada/ US)	2 (1960 – September 2015)	31 studies (87%) cross-sectional) **(Level IV)**	Cannabis for therapeutic use	Adults with psychopathology	**Anxiety disorders:** Users of cannabis for therapeutic purposes report anxiolytic motives, and an emerging literature suggest potential for treating Social Anxiety Disorder (same as noted above - *Bergamaschi et al. (2011) (N* = 36*)* & *Crippa et al. (2011) (N* = 10*)* and PTSD. However, research on other anxiety disorders is scant and the comparative effectiveness of cannabis relative to	Limited evidence (predominantly cross-sectional studies) for therapeutic cannabis use in adult psychopathology, with strongest evidence for effectiveness in PTSD.	Evidence quality was low – predominantly cross-sectional studies. Methodological quality mostly low – used Newcastle-Ottawa Scale – most ranged between 3-7 on a 10-point scale.

Reference, Year (Country)	No. of Databases (Years searched)	No. of Primary Studies (NHMRC Level of Evidence)	Intervention (control)	Population of Interest	Key Outcomes	Key Findings	SR Authors' Quality Ratings/Comments
					other pharmacological treatments for anxiety has yet to be determined. **PTSD symptoms:** ↓PTSD symptoms; ↓insomnia; ↑sleep quality; ↓nightmares; ↓hyperarousal; ↓avoidance. **Mood disorders:** The clinical implications of cannabis for therapeutic use among individuals with mood disorders are unclear.		

GRADE - Grading of Recommendations Assessment, Development and Evaluating; SR = Systematic Reviews; RCT(s) = Randomised controlled trials; PTSD = Post-traumatic Stress Disorder

6. NAUSEA AND VOMITING FINDINGS

6.1 Key findings

The only systematic reviews available on medicinal cannabis for nausea were on chemotherapy-induced nausea and vomiting. Three systematic reviews (all Level I evidence) were identified (see Table 7). Medicinal cannabis was identified to be effective for reducing nausea and vomiting in this setting, but the certainty in this evidence is low due to dated comparisons with antiemetics no longer used as standard of care.

1. Medicinal cannabis may be effective for controlling nausea and vomiting in chemotherapy patients

- Clinically meaningful improvement in controlling nausea and vomiting after chemotherapy was identified with medicinal cannabis across three systematic reviews (Level I evidence), in comparison to placebo.[22, 45, 48]
- Greater, or at least equal, control of nausea and vomiting with medicinal cannabis was found in comparison to antiemetics.[22, 45, 48]
- Patients preferred medicinal cannabis compared to antiemetics despite more adverse effects (e.g., feeling 'high' or sedated).[45]
- Specifically, oral cannabinoids (THC, Nabilone and Dronabilone) were found to be effective in controlling emesis.[45]
- While all of the studies included were RCTs (Level I evidence), there was doubt on the quality of the evidence (i.e., identified risks of bias in the studies), with some studies not in line with current reporting practices.
- Clinical application of findings is also limited with very few recent RCTs (most conducted in the 1970s and 1980s) and comparisons were made to antiemetic medication that are no longer standard of care.

6.2 Limitations and Conclusion – nausea and vomiting

While the search parameters for systematic reviews were to include nausea and vomiting more broadly, the three recent identified systematic reviews were all in relation to chemotherapy-induced nausea and vomiting (except one which also included palliative patients).[22] As with previous systematic reviews by Whiting et al. 2015[7] and the NASEM (2017) report[5] (which all cited mostly similar RCTs), the two current systematic reviews,[45, 48] and one review of systematic reviews,[22] were all very comparable. The review of systematic reviews included a meta-analysis of 7 RCTs (Level I), and the authors graded the certainty of evidence as moderate owing to serious risk of bias and serious imprecision, but the magnitude had a large effect.[22]

As with the other systematic reviews, a limitation of all but one of the RCTs reviewed in Schussel et al. (2018) were that they included antiemetics that are no longer in use (as noted above most of the studies were quite dated).[45] One study reviewed in Schussel et al. compared oral cannabinoids with a modern combination treatment of Dexamethasone and Ondansetron, reporting superior efficacy of oral cannabinoid relative to the combinatory treatment. Chow et al. 2020 also noted that a greater percentage of patients administered oral cannabinoid for chemotherapy-induced nausea and vomiting, experienced dysphoria, euphoria and sedation.[48] Therefore there is Level I evidence that medicinal cannabis may be effective for controlling chemotherapy-induced nausea and vomiting. However, the evidence was limited by dated methodology affecting relevance, the quality was deemed low to moderate, and adverse effects were frequently noted.

Table 7. *Key characteristics and findings of Systematic Reviews - Nausea and Vomiting*

Reference, Year (Country)	No. of Databases (Years searched)	No. of Primary Studies (NHMRC Level of Evidence)	Intervention (control) (participants)	Population of Interest	Key Outcomes	Key Findings	SR Authors' Quality Ratings/Comments
Allan 2018[22] (Canada)	2 (Any date to May 2017)	31 SRs of RCTs **(Level I)**	Medical cannabinoid (Placebo) (*N* = 500)	Chemotherapy patients	**Controlling nausea and vomiting. Response:** In 7 meta-analysed RCTs, 47% of medicinal cannabinoid patients had **control of nausea and vomiting** compared to 13% of placebo. RR= 3.60 (95% CI, 2.55-5.09).	There is reasonable evidence that cannabinoids improve nausea and vomiting after chemotherapy.	Authors' GRADE# rating: Moderate owing to serious risk of bias and serious imprecision, but magnitude had large effect. **Limitations:** Considerable heterogeneity –unable to explore via subgroup analyses. Heterogeneity included patient type (age, sex), tumour type, chemotherapy regimens, and cannabinoids/ antiemetics dosing.
			Medicinal cannabinoid (Antiemetic) (*N*=1,022)	Chemotherapy patients	**Controlling nausea and vomiting. Response:** in 14 RCTs, 31% of medicinal cannabinoid patients **had control of nausea and vomiting** compared to 16% of antiemetics. RR=1.85 (95% CI, 1.18 to 2.91).	Clinically meaningful improvement in controlling nausea and vomiting after chemotherapy vs. antiemetics.	Authors' GRADE rating: Low owing to serious risk of bias and serious inconsistency. **Limitations:** Same as above.
Chow 2020[48] (UK)	3 (Any date to 31 December 2018)	7 RCTs (meta-analysis) **(Level I)**	Oral cannabinoid (placebo or antiemetic) (*N* = 254)	Chemotherapy patients	**Prophylaxis for nausea and vomiting. Response:** In 7 meta-analysed RCTs, oral cannabinoids as prophylaxis against nausea and vomiting were more efficacious than placebo and antiemetics (OR = 3.45; 95% CI, 1.39 to 8.58, *p* = 0.008).	Oral cannabinoids support control for emesis - data limited, no recent RCTs, dated comparisons with antiemetic medication no longer in use. **Adverse events:** More patients with oral cannabinoids experienced dysphoria (OR = 0.17) euphoria (OR = 0.06) and	Authors commented that more current RCTs with standard reporting practices were needed. The majority of studies had either low /unclear risk of bias. **Limitations:** All but one of the RCTs reviewed included either placebos or antiemetics that are no longer used (studies quite dated).

Reference, Year (Country)	No. of Databases (Years searched)	No. of Primary Studies (NHMRC Level of Evidence)	Intervention (control) (participants)	Population of Interest	Key Outcomes	Key Findings	SR Authors' Quality Ratings/Comments
					Controlling nausea and vomiting. Response: When controlling for vomiting, oral cannabinoid was equally as efficacious as others (OR = 2.51; 95% CI: 0.33 to 19.16; *p* = 0.38). Against nausea, oral cannabinoid was equally as effective as other treatments (OR = 2.01; 95% CI, 0.49 to 8.26; *p* = 0.34)	sedation (OR = 0.30), than placebo.	
Schussel 2018[45] (Brazil)	7 (Any date to September 2017)	5 SRs of RCTs **(Level I)**	Cannabinoids (placebo or antiemetic)	Chemotherapy patients	**Controlling nausea and vomiting. Response:** more efficacious than placebo in controlling nausea; equal to prochloperazine; Cannabinoids preferred by patients.	Oral cannabinoids (THC, Nabilone, Dronabilone) were likely to have a role in controlling emesis for chemotherapy-induced nausea and vomiting. **Adverse events:** More frequent among patients treated with cannabinoids, including 'feeling high' or sedated. No greater chance of withdrawing from studies compared to other antiemetic treatment/placebo.	Authors AMSTAR review of SR: 2=Low overall quality; 2=Moderate quality; 1 High quality. Considerable overlap (81%) in SR of studies used. No good quality evidence to recommend/not the use of cannabinoids for chemotherapy-induced nausea and vomiting. **Limitations:** No recent RCTs (all conducted in the 1970s and 1980s). Dated antiemetic medication no longer in use.

GRADE - Grading of Recommendations Assessment, Development and Evaluating; RR = Risk Ratio; OR = Odds Ratio; CI = Confidence Interval; SRs = Systematic Reviews; RCT(s) = Randomised controlled trials.

7. LONG-TERM OUTCOMES AND ADVERSE EFFECTS

7.1 Safety of use and contraindications

The majority of patients using medicinal cannabis under medical supervision were not at risk and found it tolerable for long-term use.[49] Clinicians should take into consideration the characteristics of each patient and evaluate individual risks, for example males who smoke cigarettes are at increased risk for developing problems.[49] In a large prospective cohort study cannabis use was also shown to be associated with a substantial risk for developing cannabis use disorder, and a smaller risk for developing alcohol/other substance use disorders.[50] As noted below there is also a substantial risk of developing a psychotic disorder such as schizophrenia. It was contraindicated for major depressive disorder and bipolar disorder (as discussed above) as it likely worsens symptoms.[36, 43] Caution was advised for patients with cardiovascular and respiratory disorders, as well as in pregnancy and breastfeeding.[43] There was a lack of evidence in older adults, but it is likely that they have an increased vulnerability due to age- and morbidity-related decline in organ function, as well as greater likelihood of interactions with medications.[51]

7.2 Health-related quality of life

There was no significant association between general health-related quality of life and use of cannabis/cannabinoids in patients.[52] However, for pain treatment, those with multiple sclerosis and inflammatory bowel disorders reported small improvements, whereas some HIV patients reported reduced health-related quality of life.

7.3 Long-term risks and adverse events

Synthetic cannabinoid toxicity symptoms across 77 publications included tachycardia (30.2% of cases), agitation (13.5%), drowsiness (12.3%), nausea and vomiting (8.2%), and hallucinations (7.6%); with death (0.2%), stroke (0.1%) and myocardial infarction (0.09%) more uncommon.[53] A rare, but possible, scenario has also been identified, with 13 deaths from a cardiovascular mechanism associated with smoked cannabis.[46] Cannabinoid use (synthetic or natural) was also an increased risk factor for occurrence of stroke, potentially due to a genetic predisposition to neurovascular toxicity of cannabinoids in some individuals.[54]

Most studies were short-term studies, thus not demonstrating long-term risks.[27] More participants withdrew from the studies due to adverse events with cannabis-based medicines (10% of participants) than with placebo (5% of participants).[27] A review of 72 systematic reviews identified that minor adverse effects (e.g., drowsiness, dizziness, dry mouth, nausea), were reported in most studies (83%) that were comparing cannabis with placebo/active drug.[19] This was more common than serious harms (psychotic symptoms, severe dysphoric reactions, seizure, urinary tract infection). Psychiatric disturbances (e.g., mental confusion, paranoia, psychosis) occurred in 17% of participants using cannabis-based medicines, and in 5% using placebo[27]. A consistent association between cannabis use and the development of psychotic symptoms over the short- and long-term in some patients have been identified.[9] Like others,[44] researchers have also found that high cannabis exposure (i.e., more than weekly, especially daily use), high potency cannabis, and a genetic predisposition (which likely modulates it), were factors associated with an increased risk for developing psychosis, and for the earlier age onset of psychosis.[15]

Nugent et al. (2017) which used some of the same data reported in the Kansagara et al. (2017) Veteran's Affairs report (reviewed here), found low-strength evidence that light to moderate cannabis use was not associated with lung cancer, or head and neck cancer diagnoses independent of tobacco use (data were limited to case-control studies, and did not include heavy use).[9]

In a limited number of cases of heavy cannabis users, a cannabinoid hyperemesis syndrome with similar clinical presentation as cyclic vomiting syndrome (a chronic functional gastrointestinal disorder characterised by episodes of severe nausea and vomiting), has also been described - it is likely associated with use of cannabis with high THC content.[55]

7.4 Risk of harm to self or others

There was limited evidence supporting the hypothesis of risk of self-harm (suicide) or violence to others for recreational cannabis users.[25] Some authors suggest that medicinal cannabis use was associated with a decreased suicide risk in young adult men.[44] Potentially there may be a link between cannabis withdrawal and violence. Most studies linked the reduced presentation of hostility in cannabis users to its sedative nature.[44]

7.5 Neurocognitive effects

Small, short-term harmful effects on cognition in active cannabis have been identified, but long-term effects in past users were uncertain.[9] A systematic review which compared chronic[1] cannabis users with non-users found that there were low cross-sectional associations for neurocognitive impairments in chronic cannabis users (i.e., cognitive impulsivity, cognitive flexibility, attention, short-term memory, and long-term memory, but not motor impulsivity).[56] Functional and structural change have been found in chronic cannabis users' brains: neural alterations (e.g., in areas of high densities of CB1 receptors), and changed patterns of activation across brain regions.[57] The body's natural endocannabinoid system affects neural growth, differentiation, positioning and connectivity, and as such, exposure to cannabinoids such as THC may disrupt neural development (particularly during more vulnerable developmental periods such as adolescence).[57] Some limited evidence indicated that abstinence may result in reversal of cognitive decrements.[44, 57]

Age-related effects have been found in animal studies, which might be pertinent to a greater older adult population seeking medicinal cannabis: A study of old mice treated with low doses of THC exhibited reversals of age-related cognitive decline (while the same exposure in young mice resulted in cognitive decrements) – potentially due to up-regulation of the aging endocannabinoid system via increased signalling from low dose THC.[58] Additional clinical studies are warranted to confirm this.

7.6 Workplace safety

In terms of safety, Sarris et al. 2020 noted that employers have a duty of care to provide a safe and healthy workplace.[43] They commented that: "Occupational health and safety issues also exist in consideration with medicinal cannabis users. Workplace safety concerns have been raised in relation to the potential for medicinal cannabis use to impair judgment and psychomotor skills, especially in

[1] There are no standardised measures of cannabis (including different potencies) use which complicates exposure calculations

relation to motor vehicle use, operation of fixed and mobile plants particularly heavy industrial machinery, and the potential for risk-taking behaviours and those working in safety sensitive positions".

The presence of a drug or its metabolite in a person's system is not always proportional to cognitive impairment.[43] Many workplaces have workplace drug safety testing, but it does not discriminate between recreational or medicinal use, which could leave medicinal cannabis users at risk of discrimination or unfair dismissal.[43] Developing workplace risk management guidelines for medicinal cannabis, while developed in North America, is an emerging area in Australia.

8. SUMMARY AND IMPLICATIONS

This Snapshot Review summarises 17 systematic reviews published between November 2016 and March 2020, with a focus on the efficacy and safety of medicinal cannabis on chronic pain, mental health and nausea. A synthesis of the evidence is included in Table 8.

Chronic Pain

- Six recent systematic reviews were found looking at the effect of medicinal cannabis on pain.
- Medicinal cannabis may be effective for reducing general chronic and nociceptive pain (Level I evidence).
- For neuropathic pain the results around efficacy compared to placebo was discordant (Level I evidence).
- Medicinal cannabis may be effective in reducing orthopaedic pain (Level IV evidence), but low-quality research and noted potential harms limits conclusions of efficacy.
- No evidence was identified to support medicinal cannabis as a treatment for headaches and migraines.
- Where indicated as effective, the therapeutic potential of medicinal cannabis was limited by its marginal decreases in pain compared to placebo, and small response rate.
- Significant limitations to the quality of the evidence were identified, which together with potential harms and risks for adverse events, questions the potential therapeutic benefits of medicinal cannabis for these pain indications.
- Similar to the FPM[20] we also note the complex presentation of the chronic pain phenotype in a field of research in which all chronic pain syndromes are often pooled, making it more difficult to discern efficacy of medicinal cannabis. In line with this, it would be appropriate to conduct comprehensive sociopsychobiomedical assessments of patients with chronic pain, as recommended in the TGA Guidance,[1] echoed by the FPM,[20] and in line with the RACGP Guidance.[2]

Mental Health

- Ten recent systematic reviews were found where the effect of medicinal cannabis on mental health was examined.
- Medicinal cannabis may be effective (mixed Level I and IV evidence) for reducing symptoms of social anxiety disorder but the certainty in this evidence is low.
- There was mixed/inconsistent evidence that medicinal cannabis is effective for reducing symptoms of (general) anxiety disorder (Level I evidence) and post-traumatic stress disorder (Level I and IV evidence).
- Medicinal cannabis is unlikely to have any therapeutic benefit for depression (Level I evidence) and bipolar disorder (Level IV evidence), and could worsen symptoms.
- Medicinal cannabis was not associated with remission of any mental health disorders.
- Medicinal cannabis for mental health indications is an emerging area, characterised by a lack of well-controlled and high-quality studies focused on specific clinical populations.
- It is not indicated as a treatment option by Phoenix Australia (Centre for Posttraumatic Mental Health) for PTSD, who noted that medication was not considered as routine first-line treatment for PTSD (the preference is for psychological therapy).[13] Where medication was considered for PTSD, SSRI antidepressants were indicated as the first choice medication.[13]

Nausea and vomiting

- This review of three recent systematic reviews (Level I evidence) indicated that medicinal cannabis may be effective for reducing chemotherapy-induced nausea and vomiting. However, it should be noted that the reviews were mostly based on dated trials, and compared antiemetics which are no longer standard of care today.
- Considerable overlap was noted in the studies included in the systematic reviews, as has been previously identified.[2, 5, 7, 14]
- It should be noted that other groups are also not indicating it as first-line treatment. Abrahms (2018) in his update on the NASEM report noted that the American Society for Clinical Oncology Expert Panel on Antiemetics, recently issued updated guidelines and recommended: "FDA-approved cannabinoids dronabinol or nabilone to treat nausea and vomiting that is resistant to standard antiemetic therapies. Evidence remains insufficient to recommend marijuana in this setting".[8]

Conclusion

This Snapshot Review found that medicinal cannabis may be effective (Level I evidence) in reducing chronic and nociceptive pain, for controlling chemotherapy-induced nausea and vomiting (Level I evidence), and for reducing symptoms of social anxiety disorder (Level I and IV evidence). There was inconsistent evidence for its effectiveness in reducing neuropathic pain (Level I evidence), for reducing symptoms of (general) anxiety disorder (Level I evidence), and for treating symptoms of post-traumatic stress disorder (Level I and IV evidence). We found limited evidence (Level IV) for medicinal cannabis reducing orthopaedic pain, and no evidence for reducing pain associated with headaches/migraines. It is likely to be contraindicated for depression (Level I evidence) and bipolar disorder (Level IV evidence), and not associated with remission of mental health disorders.

In general, the field of medicinal cannabis was plagued by low quality evidence. It lacked long-term impact studies, and was only an emerging field of research in mental health. There were well-described potential harms and increased risks for adverse events, which raise questions around safety. Great variability in formulations, dosage, routes of administration and therapeutic range were noted, which makes it challenging to draw firm and consistent conclusions around its efficacy. Thus, we conclude that its safety and efficacy is limited, particularly as first-line treatment, for chronic pain, mental ill health, and nausea and vomiting.

Table 8. *Synthesis of Evidence*

Condition Treated	Our Findings (Level of Evidence)	Limitations & Comments
Chronic pain	May be effective (Level I)	Moderately efficacious for treatment of chronic pain, but beneficial effects may be offset by potentially serious harms. Certainty of evidence low as serious risk of bias in studies; evidence insufficient to make well-founded conclusions about clinical advantage including safety and tolerability.
Neuropathic pain	Discordant results (Level I)	Predominantly showed efficacy relative to placebo, but reductions in pain of ≥30% to ≥50% were achieved by small numbers of patients. One systematic review found inconsistent evidence. Evidence was low/insufficient in most studies; studies small. Harms may outweigh the potential benefits.
Nociceptive pain	May be effective (Level I)	Evidence limited to few studies. Efficacy equal to codeine, but depressant effect on central nervous system; evidence insufficient to make well-founded conclusions about clinical advantage.
Orthopaedic pain	May be effective (Level IV)	Minimal high-quality evidence. Efficacy (post-trauma, post-surgery, back pain, arthritis) only demonstrated when compared with placebo; evidence insufficient to make well-founded conclusions about clinical advantage.
Headaches/ Migraines	No evidence	No systematic reviews identified. One RCT of Nabilone showed efficacy for medication overuse headaches. Lack of evidence and insufficient grounds for medicinal cannabis' clinical advantage.
PTSD symptoms	Discordant results (Level I & IV)	Systematic reviews with RCTs cite the same small study, and field further limited to clinical case studies; Nabilone might ↓nightmares & ↑sleep, but notable adverse event rates; Not indicated as first-line treatment for PTSD (Phoenix Australia).
(General) Anxiety disorder symptoms	Discordant results (Level I)	One systematic review - small improvement in symptoms of anxiety among individuals with other medical conditions (e.g., Pain); One systematic review inconclusive. Quality of evidence low – small sample sizes, high risk of bias.
Social anxiety disorder symptoms	May be effective (Level I & IV)	Emerging field. Small number of positive studies (most systematic reviews cite the same two small RCTs on social anxiety). Low quality evidence that THC (with or without CBD) ↓anxiety and social anxiety disorder symptoms. More RCTs needed to show clinical advantage.
Depression disorder symptoms	Contraindicated/ worsens symptoms (Level I)	Level I evidence that medicinal cannabis does not improve symptoms of depression. Beyond this Level I evidence data in the field is limited to case studies/depression not being the primary clinical presentation. Level IV (longitudinal) evidence that likely to worsen symptoms. From available evidence contraindicated as treatment for Major Depressive Disorder.
Bipolar disorder symptoms	Contraindicated/ worsens symptoms (Level IV)	Scant information. No therapeutic benefit; likely to worsen symptoms. From available evidence contraindicated as treatment.
Chemotherapy-induced nausea and vomiting	May be effective (Level I)	Clinically meaningful improvement in controlling nausea and vomiting in comparison to placebo and antiemetics. Limited to chemotherapy-induced nausea & vomiting; not compared to current antiemetics; preferred by patients despite adverse effects; potentially has a role if treatment resistant, but evidence remains insufficient to make recommendation.

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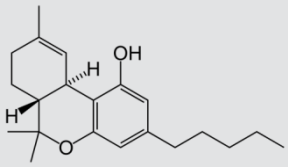
APPENDIX 1: OVERVIEW OF CANNABINOIDS

Cannabinoids

- Chemicals which link the body's natural endocannabinoid system with receptors CB1 and CB2 in the body and brain, having similar effects as by those produced by *Cannabis sativa.*[2]
- The body's endocannabinoid system plays a central role in homeostasis and neuroplasticity, including formation of neurons and refinement of neuronal connections.[57]
- The cannabinoids that people use can be recreational, medicinal or synthetic. One of the current major issues of cannabis for the treatment of a range of conditions, including chronic pain, is the overlap of medicinal and recreational use, particularly in light of greater legalised access.[49]

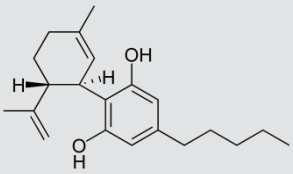
Two main types of cannabinoids

Delta-9-tetrahydrocannabionol (THC)



- high doses can cause psychotropic side effects such as alteration of time, lack of concentration, feeling drunk, feeling high, anxiety, paranoia, depression, hallucinations, dissociation, disturbance of thoughts and euphoria[28]
- believed to be effective as a medicinal product at lower doses[49]
- Nabilone and Dronabinol are pharmaceutical grade THC extracts approved by the FDA

Cannabidiol (CBD)



- non-intoxicating[32]
- diverse range of therapeutic properties[32]
- favourable toxicity profile[32]
- potential side-effects are generally mild/infrequent[32]
- no evidence for dependency or abuse potential[3]

Some medicinal formulations combine both THC and CBD, and Romero-Sandoval et al. (2018) noted that "CBD may reduce unwanted psychotropic effects of THC and potentiate other effects (i.e., anticonvulsant, analgesic etc.) when given concomitantly".[49]

[2] https://adf.org.au/drug-facts/cannabinoids/

APPENDIX 2: SPECIFIC INCLUSION AND EXCLUSION CRITERIA USED IN EVIDENCE REVIEW

Criteria	Inclusion	Exclusion
Patient/ population	Adults; chronic non-cancer pain (including neuropathic pain); mental health problems where medicinal cannabis is used as treatment (e.g., for mood and anxiety disorders including PTSD); nausea and vomiting	Children; cancer-pain; multiple sclerosis (MS) associated pain; experimental pain; rheumatic arthritis; osteoarthritis; autoimmune diseases including fibromyalgia; personality disorders; psychoses and schizophrenia; treatment for substance use disorders (e.g., alcohol, smoking cigarettes), cannabis substance use disorder; cannabis-induced mental health problems (e.g., substance-induced psychosis); epilepsy; neurodegenerative conditions including Alzheimer's disease, dementia, multiple sclerosis and spasticity; movement disorders including dystonia, Huntington's disease, Parkinson's disease, Tourette syndrome; Crohn's disease, ulcerative colitis, inflammatory bowel disease (IBD); cannabinoid-induced hyperemesis; palliative care; insomnia
Intervention / indicator	Medicinal cannabinoid (including cannabidiol and/or delta-9-tetrahydrobannabidiol – plant-based, whole plant extracts or synthesised cannabinoids)	Recreational use of cannabis; edibles; smoked cannabis
Comparison/ control	Standard care or comparison to placebo (sham) or active comparator	N/A
Outcomes	Pain: Reduction in pain intensity; general improvement in quality of life Nausea: Control of nausea and vomiting Mental health: reduction in symptoms; improvement in functioning; remission General: adverse events/effects	N/A
Setting	Clinical and research (in-patient or out-patient, randomised controlled trials)	Patients in a long-term care facility**.**
Study Design	Systematic reviews which include randomised controlled trials	Non-systematic reviews, cohort studies, case control studies, case series, editorials, letters, conference abstracts and commentaries
Publication details	English language studies on humans	Non-English studies, animal studies
Time period	Research published between 1 November 2016 – 3 March 2020	Research published pre-November 2016