McMaster University | HEALTH FORUM

Rapid Evidence Profile

Reviewing the effectiveness of cannabis on symptoms of select conditions

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Context

- Legislative changes in Canada in 2014 and 2017 have led to substantial increases in medical authorizations for cannabis.
- Veterans are disproportionately affected by conditions for which medical cannabis treatment is often pursued, such as post-traumatic stress disorder (PTSD) and chronic pain.
- As of 2016, Veterans Affairs Canada's reimbursement policy for cannabis for medical purposes established a maximum three-gram-per-day limit at a fixed rate of reimbursement.
- This rapid evidence profile reviews the evidence on the effectiveness of cannabis of alleviating symptoms from select conditions and examines medical authorization and reimbursement policies in comparator countries including each of the 'Five Eyes' countries, Israel and the Netherlands.

+ Global evidence drawn upon

Evidence syntheses selected based on relevance, quality and recency of search

+ Forms of domestic evidence used (🍁 = Canadian)

Data analytics | Evaluation | Qualitative insights | Guidelines

+ Other types of information used

Jurisdictional scan (seven countries: Australia, Canada, New Zealand, United States, United Kingdom, the Netherlands, Israel)

*** Additional notable features**

This rapid synthesis was prepared in five business days using an 'all hands on deck' approach.

Questions

- What are the effects of cannabis on anxiety, chronic pain, depression, PTSD and sleep disorders?
- Which compositions (specifically CBD versus THC), routes of administration, dosages and frequency of use are most effective for symptom reduction for these conditions?
- Under what criteria (e.g., conditions and compositions) is cannabis medically authorized and/or reimbursed for Veterans in each of the 'Five Eyes' countries as well as in Israel and the Netherlands?

High-level summary of key findings

- We found 33 evidence syntheses (of which we determined 29 to be highly relevant, three of medium relevance and two of low relevance), one guideline based on a recent high-quality overview of reviews (soon to be published), and three single studies with findings specific to Canadian Veterans.
- While we identified a significant amount of literature, most of the evidence syntheses describe challenges with the quality of the evidence included, largely because of heterogeneity within the literature with respect to composition of cannabis (e.g., different cannabis products), form of administration of cannabis, dosage and timing of use.

- The identified literature covers all conditions of interest as well as many different forms of cannabis, including both synthetic and natural forms of CBD, THC and forms of cannabis with CBD and THC in equivalent amounts.
- In general, there remains insufficient evidence to determine the effectiveness of cannabis for alleviating symptoms of mental health conditions, with much of the included evidence reported as low and moderate certainty.
- Despite this, there are some promising findings with respect to:
  - the effects of CBD on reducing symptoms of social anxiety disorder
  - the effects of THC on reducing symptoms of chronic non-cancer pain
  - the effects of nabilone and dronabinol on reducing nightmares and other symptoms of PTSD
- While most evidence syntheses identified dosages, very few findings specifically addressed dose-response relationships and we were unable to identify any findings assessing frequency of use.
- For jurisdictional scans, only two countries – Australia and Canada – had specific medicinal cannabis reimbursement programs for Veterans, while other countries– Israel, New Zealand and the U.K. – maintain reimbursement programs for the general population that may also be accessed by Veterans.

Box 1: Approach and supporting materials

We identified evidence addressing the question by searching Health Systems Evidence and PubMed and PsychInfo. All searches were conducted on 4 January 2023. The search strategies used are included in Appendix 1. In contrast to synthesis methods that provide an in-depth understanding of the evidence, this profile focuses on providing an overview and key insights from relevant documents.

We searched for full evidence syntheses (or synthesis-derived products such as overviews of evidence syntheses) and protocols for evidence syntheses.

We appraised the methodological quality of evidence syntheses that were deemed to be highly relevant using AMSTAR. AMSTAR rates overall quality on a scale of 0 to 11, where 11/11 represents a review of the highest quality. The AMSTAR tool was developed to assess reviews focused on clinical interventions, so not all criteria apply to evidence syntheses pertaining to delivery, financial or governance arrangements within health systems or to broader social systems.

A separate appendix document includes:
1) methodological details (Appendix 1)
2) summary table of the key findings from evidence syntheses and single studies (Appendix 2)
3) details about each identified synthesis (Appendix 3)
4) details from single studies (Appendix 4)
5) details from jurisdictional scan (Appendix 5)
6) documents that were excluded in the final stages of review (Appendix 6).

This rapid evidence profile was prepared in the equivalent of five days of a 'full-court press' by all involved staff.

Framework to organize what we looked for

- Conditions
  - Anxiety
  - Chronic pain
  - Depression
  - PTSD
  - Sleep disorders
- Composition
  - Natural
  - Semi-synthetic
  - Synthetic
- Routes of administration
  - Oral
    - Oils and oral solutions

        - Edible
    - Oro-mucosal and intranasal
    - Smoked
    - Suppository
    - Topical
    - Vaporized
- Dosage
    - High (greater than 10.0 mg)
    - Medium (5.0 mg to 10.0 mg)
    - Low (less than 5.0 mg)
- Frequency of use
    - Two or more times per day
    - Daily
    - As needed
- Outcomes
    - Health outcomes
        - Symptom reduction
        - Adverse events
    - Consumer experiences
    - Provider experiences
    - Cost

What we found

We found 33 evidence syntheses (of which we determined 29 to be highly relevant, three of medium relevance and two of low relevance), one guideline based on a recent high-quality overview of reviews (soon to be published), and three single studies with findings specific to Canadian Veterans.

Coverage by and gaps in existing evidence syntheses

While we identified a significant amount of literature, most of the evidence syntheses describe challenges with the quality of the evidence included. This is largely a result of the heterogeneity within the literature with respect to composition of cannabis (e.g., different cannabis products), form of administration of cannabis, dosage and timing of use. The result is there being no findings based on high certainty evidence (using a GRADE approach).

The identified literature covers all conditions of interest in the framework above as well as many different forms of cannabis and THC:CBD ratios, including both synthetic and natural forms of CBD, THC (including those with very high percentages of THC >98% as well as synthetic forms such as nabilone and dronabinol), and forms of cannabis with CBD and THC in equivalent amounts (including synthetic forms such as nabiximols). Despite the literature including both natural and synthetic forms of cannabis, no included evidence synthesis or single study provided a sub-analysis that compared the effectiveness between the two types.

With respect to routes of administration, much of the identified evidence focuses on orally consumed cannabis, with relatively less addressing oro-mucosal, inhaled (either smoked or vaporized) and topical use. While most evidence syntheses identified dosages reported in the included studies, very few findings specifically addressed dose-response relationships largely because of the significant ranges reported. We did not identify any findings comparing frequency of use.

All but one recent medium-quality evidence synthesis and two single studies addressed health outcomes, which examined care experiences. We did not identify any findings related to provider experiences or costs.

The literature, except for one recent high-quality and one recent medium-quality evidence syntheses, focused on short-term outcomes (e.g., less than 4 months).(1; 2)

Finally, a critical gap that was noted in one recent high-quality and one recent medium-quality evidence syntheses is the lack of ethnic or racial diversity in the reported samples of single studies included in evidence syntheses, further challenging the generalizability of findings.(2; 3) The recent medium-quality evidence synthesis reported that non-white individuals are less willing to use medicinal cannabis as a treatment option when compared to white individuals.(3)

What do existing evidence syntheses, guidelines and highly relevant single studies tell us about the effects of cannabis on anxiety, chronic pain, depression, PTSD and sleep disorders on equity-centred quadruple aim?

Included evidence documents addressed two of the four equity-centred quadruple-aim metrics – health outcomes and, to a lesser extent, care experiences. We did not identify any evidence documents that included findings relevant to either provider experiences or per-capita costs. Below, we synthesize the included evidence by condition. Additional insights are available in Appendices 2, 3 and 4.

Anxiety

Five recent medium-quality evidence syntheses reported a short-term reduction in anxiety levels among those with diagnosed anxiety disorders (i.e., generalized anxiety disorder, social anxiety disorder) following the use of orally administered (capsule or sublingual spray) CBD.(4-8) However, following a sub-population analysis, one of the evidence syntheses determined these findings not to be significant.(7) Three of the evidence syntheses specified that these findings were for social anxiety disorder and may not apply across all types of anxiety.(4-6)

One of the syntheses also found that nabiximols reduced symptoms of social anxiety disorder.(6) Though a recent high-quality review found cannabinoids with equal levels of CBD and THC reduced anxiety compared to placebos but did not result in a significant improvement against active comparators.(9)

Chronic pain

Mixed evidence was found for the effects of cannabis on chronic pain, with the certainty of this evidence graded as being low-to-moderate. One recent high-quality living evidence synthesis, as well as two recent high-quality and seven recent medium-quality evidence syntheses, indicate that cannabis use may result in small reductions in chronic non-cancer pain,(2; 7; 10-16) while two recent medium-quality evidence syntheses describe cannabis has having limited effects.(1; 13)

One recent high-quality and one recent medium-quality evidence syntheses found products with high or equal THC to CBD ratios have a greater effect on pain severity, but are also associated with an increase in adverse events and withdrawal in trials.(11; 12) Mixed effectiveness was reported for the long-term use of CBD for chronic pain, with one recent high-quality evidence synthesis reporting daily consumption to have reduced chronic non-cancer pain over the long-term, while a second synthesis (recent medium-quality) reported no evidence of pain reduction over the long-term, with the exception of individuals with fibromyalgia who experienced small improvements.(1; 2)

Interestingly, two recent medium-quality evidence syntheses note that the benefit of cannabis for chronic pain reported in randomized controlled trials and observational studies is substantially lower than the perceived benefit reported by those using cannabis in qualitative studies.(1; 13) One recent medium-quality evidence synthesis of qualitative studies and two qualitative single studies of Canadian Veterans found that despite mixed willingness to

try medicinal cannabis, those that did reported a reduction in pain and ease of other symptoms including improved sleep, improved relationships with friends and families and improved symptom management.(3; 17; 18)

These findings are consistent with soon-to-be released Canadian guidelines for cannabis and chronic pain, which recommend that in instances where the standard of care (i.e., first-line treatment) is not sufficient, providers may offer a trial of cannabis for medical purposes, conditional on shared decision-making.

With respect to care experiences, one recent medium-quality evidence synthesis and three single studies of Canadian Veterans examined preferences and experiences using cannabis for chronic pain.(3; 17-19) The recent medium-quality evidence synthesis and two single studies reported a preference for the use of cannabis over other treatments, namely prescription opioids.(3; 17; 18) One of the single studies of Canadian Veterans described funding for cannabis as being easy to access but reported difficulty in finding family physicians or accessing healthcare services to be a barrier to medicinal cannabis use.(17) The same single study also reported that Veterans expressed concern about the insufficient guidance available from medical professionals and cannabis suppliers on safe use as well as continued stigma from the public.(17)

Depression

Mixed and negative findings were reported on the effects of cannabis use for depression. One recent medium-quality evidence synthesis found no effect from CBD on depressive symptoms but small improvements from nabiximols when compared to a placebo.(7) In contrast, a second recent medium-quality evidence synthesis found no effect of nabiximols on symptoms of depression and suggested that high doses may worsen depressive symptoms.(20) Similarly, one low-quality evidence synthesis found cannabis use (both medicinal and recreational) to be associated with worsened courses of major depressive disorder.(21) Though a recent medium-quality review reported uncertain results on the effects of cannabis on the clinical course of depression.(22)

Post-traumatic stress disorder

Similar to chronic pain, there is a considerable amount of literature about the effects of cannabis on PTSD, with much of it providing inconclusive results.(15; 23) Despite overall uncertainty about the effects of cannabis, four recent medium-quality reviews found THC-based synthetics such as nabilone and dronabinol improved some PTSD symptoms, namely nightmares, when compared to a placebo. However, one of the medium-quality evidence syntheses found health risks associated with these products including THC-related cognition dysfunction and risk of psychosis.(7; 22; 24; 25) One recent medium-quality review found cannabis use may be linked to the onset of PTSD in individuals that have previously experienced trauma.(22)

Sleep disorders

Two recent medium-quality evidence syntheses found limited evidence to support the use of cannabis therapies for either primary or secondary sleep disorders and that any relatively small improvements should be weighed against adverse events.(26; 27) However, one recent medium-quality evidence synthesis found CBD to be beneficial in the management of co-morbid insomnia in patients with chronic pain and PTSD,(28) and two recent high-quality and one recent medium-quality evidence synthesis found nabilone improved sleep scores when compared to a placebo.(7; 26; 29) Similarly, one recent low-quality evidence synthesis found THC and THC-based products (such as nabilone) showed more promise at improving sleep than other forms of cannabis.(30) The synthesis also noted that this conclusion is based on low-certainty evidence due to the heterogeneity in timing and dosages.(30)

Adverse events

Minor adverse events were reported in most of the included evidence documents. One recent medium-quality and one recent high-quality evidence syntheses that did not differentiate between types of cannabis products found low-certainty evidence that minor adverse events associated with cannabis use are common, but serious adverse events

are rare.(26; 31) Common adverse events tended to include dizziness, drowsiness, dry mouth, fatigue and nausea. In one recent medium-quality evidence synthesis, CBD was reported to have mild to moderate adverse effects, with the most common being drowsiness, sedation, fatigue, dizziness, headache, diarrhoea, nausea, decreased appetite and abdominal discomfort.(32) Two recent medium-quality evidence syntheses reported higher rates of adverse events from cannabis products with higher amounts of THC.(9; 14) Finally, one recent medium-quality evidence synthesis noted that greater numbers of adverse events were reported in studies with longer follow-up periods (i.e., over 24 weeks).

Though the majority of included evidence documents identified adverse events generally, one recent medium-quality evidence synthesis and one older medium-quality evidence synthesis examined adverse effects in relation to particular conditions.(26; 18) Both evidence syntheses identified that cannabis use was associated with worsened courses and functioning of individuals with bipolar disorder, but found conflicting results with respect to the effect of cannabis on depressive symptoms.(26; 18) The older medium-quality evidence synthesis described that continued cannabis use may increase the odds of developing PTSD, but this finding was based on a small number of included studies and has not been replicated in other evidence syntheses.(26)

What do existing evidence syntheses, guidelines and highly relevant single studies tell us about the effects of different compositions, routes of administration, dosages and frequency of use on the effectiveness of symptoms reduction for anxiety, chronic pain, depression, PTSD and sleep disorders?

Where available, findings related to composition and their relative effectiveness on symptom alleviation have been reported in the section above. While most of the tables describing characteristics of included studies in the evidence syntheses provided information on routes of administration and dosages, this was not the explicit focus of any of the included documents and was also very rarely reported in ways that allowed for comparison. The few identified findings are reported below. We did not identify any findings related to frequency of use.

Dosages

Significant variation in dosages of different compositions of cannabis were reported in the identified literature. Where possible these ranges have been included in the data extraction in Appendix 3. We did not identify any evidence syntheses that explicitly examined the dose-response relationship for different compositions of cannabis.

We did identify two specific findings related to dosage. One recent medium-quality evidence synthesis identified that single doses of CBD ranging from 300 to 600 mg were effective in reducing symptoms of social anxiety disorder.(5) One recent high-quality review found medicinal CBD dosages ranging from 39 mg to 1.5 g per day resulted in reduced symptoms of chronic non-cancer pain.(2)

Routes of administration

Similarly to dosage, we did not identify any evidence syntheses that explicitly compared routes of administration, but information was frequently reported in tables in evidence syntheses describing characteristics of included studies. With respect to routes of administration, much of the identified evidence focuses on orally consumed cannabis, with relatively less addressing oro-mucosal, inhaled (either smoked or vaporized) and topical use. Findings related to adverse events and potential harms from cannabis use did not differentiate between routes of administration. Where possible the different routes of administration noted in evidence syntheses have been included in the data extraction in Appendix 3.

One recent high-quality and two recent medium-quality evidence syntheses found that when medicinal cannabis is orally consumed (as opposed to when inhaled), it may result in very small reductions in chronic-cancer and non-cancer pain, as well as very small improvement in physical functioning and sleep quality.(14-16) This is consistent with findings from soon-to-be released Canadian clinical guidelines on cannabis use and chronic pain, which

recommend that non-inhaled forms of cannabis be offered first to people living with chronic cancer or non-cancer pain where the decision has been made to offer a trial of cannabis for medical purposes.

Though not related to effectiveness, one recent medium-quality evidence synthesis examining the preferences of medicinal cannabis used found women tended to prefer topical preparations as opposed to inhaled.(3)

Experiences from Five Eyes countries as well as Israel and the Netherlands

For the jurisdictional scan, we looked at the federal level in each of the 'Five Eyes' countries – Australia, Canada, New Zealand, U.K., and U.S. – as well as Israel and the Netherlands to identify the criteria for authorizing and funding medicinal cannabis for Veterans.

We were only able to identify cannabis reimbursement programs specific to Veterans in Australia and Canada. In Australia, medicinal cannabis may be covered for Veterans if prescribed by a treating physician for chronic pain; chemotherapy-induced nausea and vomiting; palliative care indications; anorexia and wasting associated with chronic illnesses such as cancer; spasticity from neurological conditions; and some types of epilepsy. Cannabis is considered to be a second second-line treatment after standard therapy has been deemed unsuccessful. Medical cannabis is funded through the Repatriation Pharmaceutical Benefits Scheme, under which there is a two-tier classification system, whereby tier 1 may be applied over the phone while tier 2 requires a written assessment from a treating non-GP specialist confirming that medicinal cannabis would clinically benefit the patient. Tier 1 criteria include:

- the client is receiving a maximum of two products at any one time
- the client is receiving any product or products containing the equivalent, or less, of a total of 40 mg per day of THC or no THC
- the client has a health condition (see above) where there is an already established treatment supported under the framework.

Tier 2 criteria include:

- the client is receiving three or more products at any one time
- the client is receiving any product or products that contain a total of over 40 mg per day of THC
- for conditions where there is an already-established treatment but where either of the two tier 2 circumstance above exist
- for conditions not listed above where the application would need to cite evidence (from multiple high-quality studies) to support efficacy of the proposed treatment.

In Australia, medicinal cannabis is covered under health insurance with the exception of a concessional co-payment, which needs to be paid to the pharmacy each time medical cannabis is dispensed, unless the patient has reached the concessional safety net limit meaning no further costs for the calendar year can be incurred.

In Canada, the reimbursement policy from Veterans Affairs Canada has established a maximum three-gram-per-day limit of dried cannabis or its equivalent in fresh marijuana or cannabis oil**.** Veteran's Affairs established a fixed rate of reimbursement of up to $8.50 per gram. Veterans entitled to a Veterans Affairs Canada Disability Pension, Disability Award or Pain and Suffering Compensation are eligible for the cost of treatment for their disability benefits entitled condition.

In New Zealand and the U.K., we were able to identify policies for medicinal cannabis for the general population that are also open to Veterans. In New Zealand, the medicinal cannabis scheme came into effect in April 2020 and is available for members of the general population that have obtained a prescription by a physician. Medicinal cannabis products can be prescribed so long as they have been approved for distribution under the *Medicines Act* for specific indications. Though access to medicinal cannabis is permitted under select circumstances, no cannabis products are currently funded by the New Zealand Pharmaceutical Management Agency and are not being

recommended as first-line treatment for any indication. Similarly, in the U.K., medicinal cannabis has been approved and is reimbursed (except for a dispensing fee) for select conditions, namely children and adults with rare forms of epilepsy, vomiting and nausea associated with chemotherapy, and people with muscle stiffness and spasms caused by multiple sclerosis. NICE currently recommends against the use of cannabis-based products to manage chronic pain.

In Israel, we identified that Veterans are eligible for a medicinal cannabis license provided by a certified doctor but were unable to identify the relevant conditions for which these licenses are permitted or the associated reimbursement policies. In the Netherlands, as of 1 January 2020, the use of medicinal cannabis is no longer reimbursed for Veterans or military personnel. Finally, in the U.S., as cannabis remains an illegal substance at the federal level, the Department of Veterans Affairs is required to follow federal laws and, as a result, does not reimburse any cannabis for medicinal use. However, the policy is clear that if a Veteran resides in a state that permits the legal use of cannabis, this will not interfere with health insurance offered through the Veterans Affairs system.

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