OBJECTIVE
Primary care physicians can incorporate medical cannabinoids into their prescribing practices by being informed with best available evidence and using a simplified, shared decision-making approach with their patients.

TARGET POPULATION
Adults (i.e., 18 years of age and older)

EXCLUSIONS
Children

RECOMMENDATIONS
See recommendations summary algorithm in Appendix A.

GENERAL RECOMMENDATION
X DO NOT prescribe medical cannabinoids for most medical conditions. There is a lack of evidence of benefit, and known harms. [Strong recommendation]

Note: Possible exceptions are described elsewhere in this document for some types of pain, chemotherapy-induced nausea and vomiting, and spasticity due to multiple sclerosis or spinal cord injury.

MANAGEMENT OF PAIN

ACUTE PAIN
X DO NOT prescribe medical cannabinoids for acute pain management, due to evidence of no benefit and known harms. [Strong recommendation]

HEADACHE
X DO NOT prescribe medical cannabinoids for headache, due to the lack of evidence and known harms. [Strong recommendation]

RHEUMATOLOGIC PAIN
X DO NOT prescribe medical cannabinoids for pain associated with rheumatologic conditions (including osteoarthritis and back pain), due to the lack of evidence and known harms. [Strong recommendation]

Recommendations against “due to the lack of evidence” also include consideration of the high probability of harms identified in all cannabinoids.

These recommendations are systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances. They should be used as an adjunct to sound clinical decision making.
NEUROPATHIC PAIN

✗ DO NOT prescribe medical cannabinoids as first- or second-line treatments in neuropathic pain, due to limited benefits and high risk of harms. [Strong recommendation]

✓ Consider medical cannabinoids for refractory neuropathic pain, with the following considerations: [Weak recommendation]
  - Discuss the benefits and risks of medical cannabinoids for pain with the patient
  - Patients have had a reasonable therapeutic trial\(^b\) of ≥3 prescribed analgesics,\(^c\) and have persistent problematic pain despite optimized analgesic therapy.
  - Medical cannabinoids are adjuncts to other prescribed analgesics.

PALLIATIVE (END OF LIFE) CANCER PAIN

✗ DO NOT prescribe medical cannabinoids as first- or second-line for palliative cancer pain, due to limited benefits and high risk of harms. [Strong recommendation]

✓ Consider medical cannabinoids for refractory pain in palliative cancer patients, with the following caveats: [Weak recommendation]
  - Patients have had a reasonable therapeutic trial\(^b\) of ≥2 prescribed analgesics, and have persistent problematic pain despite optimized analgesic therapy.
  - Medical cannabinoids are adjuncts to other prescribed analgesics.

TYPES OF MEDICAL CANNABINOIDS FOR PAIN

✓ Do use a pharmaceutically developed product (nabilone or nabiximols) as the initial agent if considering medical cannabinoids. [Strong recommendation]

Table 1: Types of Medical Cannabinoids for Pain

<table>
<thead>
<tr>
<th>TYPE</th>
<th>CONSIDERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nabilone</td>
<td>- Used off-label for pain and has limited evidence of benefit</td>
</tr>
<tr>
<td></td>
<td>- Less expensive than nabiximols and dosing is more consistent than smoked cannabis</td>
</tr>
<tr>
<td>Nabiximols</td>
<td>- Expensive and, in some provinces, only available through specialist prescribing or special authorization.</td>
</tr>
<tr>
<td></td>
<td>- Nabiximols have better evidence than nabilone.</td>
</tr>
</tbody>
</table>

✗ DO NOT prescribe medical marijuana (particularly smoked) as the initial product if considering medical cannabinoids. [Strong recommendation]

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\(^b\) Reasonable therapeutic trial is defined as six weeks of therapy with: appropriate dose, dose titration, and monitoring (e.g., function, quality of life).

\(^c\) Other prescribed therapies for neuropathic pain management include, but are not limited to (in no particular order): tricyclic antidepressants (e.g., amitriptyline, nortriptyline), gabapentinoids (gabapentin, pregabalin) or SNRI antidepressants ( duloxetine, venlafaxine). The committee felt that ≥3 medications should be trialed before considering cannabinoids or opioids.
MANAGEMENT OF NAUSEA AND VOMITING

GENERAL

× DO NOT prescribe medical cannabinoids for general nausea/vomiting, due to the lack of evidence, and known harms. [Strong recommendation]

PREGNANCY

× DO NOT prescribe medical cannabinoids for nausea/vomiting in pregnancy or hyperemesis gravidarum due to the lack of evidence, known harms and unknown harms. [Strong recommendation]

CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING (CINV)

× DO NOT prescribe medical cannabinoids as first- or second-line therapy for CINV due to limited comparisons with first-line agents, and known harms. [Strong recommendation]

✓ Consider medical cannabinoids for treatment of refractory CINV, with the following caveats: [Weak recommendation]
  o Discuss the risks and benefits of medical cannabinoids for CINV with the patient.
  o Patients have had a reasonable therapeutic trial of standard therapies, and have persistent CINV.
  o Medical cannabinoids are adjuncts to other prescribed therapies.

TYPES OF MEDICAL CANNABINOIDS FOR CINV

✓ DO prescribe nabilone if considering a medical cannabinoid. [Strong recommendation]

× DO NOT prescribe nabiximols and medical marijuana (smoked, oils or edibles) as they are inadequately studied. [Strong recommendation]

Note: while dronabinol has been studied, it is no longer available in Canada.

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\[d\] Other prescribed therapies for CINV include, but not limited to (in no particular order): serotonin antagonists (e.g., ondansetron), neurokinin-1 receptor antagonists (aprepitant, fosaprepitant), corticosteroids (dexamethasone), and dopamine antagonists (prochlorperazine, metoclopramide).
**MANAGEMENT OF SPASTICITY**

**GENERAL**

X DO NOT prescribe medical cannabinoids for general spasticity, due to the lack of evidence and known harms. [Strong recommendation]

**SPASTICITY IN MULTIPLE SCLEROSIS (MS)/SPINAL CORD INJURY**

X DO NOT prescribe medical cannabinoids as first- or second-line therapy for spasticity in MS/Spinal Cord Injury due to limited evidence and known harms. [Strong recommendation]

✓ Consider medical cannabinoids for refractory spasticity in MS/Spinal Cord Injury, with the following caveats: [Weak recommendation]
  - Discuss the benefits and risks of medical cannabinoids for spasticity with the patient.
  - Patients have had a reasonable therapeutic trial of standard therapies (including non-pharmaceutical measures), and have persistent spasticity.

**TYPES OF MEDICAL CANNABINOIDS FOR SPASTICITY**

✓ Do prescribe nabiximols if considering medical cannabinoids. [Strong recommendation]

✓ DO NOT prescribe medical marijuana (smoked, oils or edibles) as they are inadequately studied. [Strong recommendation]

✓ May consider nabilone given its lower cost; however, it is off-label and lacks evidence for this use. [Weak recommendation]

**BACKGROUND**

In Canada, 43% of people aged 15 years and older have used cannabis in their lifetime, with 12% using cannabis in the last year. \(^1\) Men use cannabis more commonly than women (16% versus 8%), with the highest use in those aged 18-24 years (33%). \(^1\) Among marijuana users in the United States (US), the most commonly reported reason for use was recreational in 53%, medicinal in 11%, and a mix in 36%. \(^2\) In many countries, including Canada, self-reported medical marijuana use, here defined as dried cannabis or cannabis oil, is often in the range of 15-19% for conditions like multiple sclerosis (MS), chronic pain, and inflammatory bowel disease. \(^3\) The most common reason for medical marijuana use is chronic pain, varying from 58-84% of medical marijuana users. \(^3\) Other reasons include mental health concerns (such as anxiety), sleep disorders, and spasticity in MS. \(^3\) Surveys of medical marijuana users find ≥70% believe medical marijuana use results in moderate or better improvement in their symptoms. \(^3\) A Canadian study found that functional status among medical marijuana users was worse than the general population, reporting scores of 28 versus 7 on functional assessment (World Health Organization Disability Assessment Schedule, score 0-100 with higher scores being worse function). \(^4\)

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\(^{n}\) Other therapies for spasticity in MS include, but not limited to (in no particular order): daily stretching, range-of-motion exercises, baclofen, gabapentin, tizanidine, dantrolene, benzodiazepine, or botulinum toxin.
Medical marijuana use in Canada has grown sharply. On average, the number of registered medical marijuana users in Canada has approximately tripled every year since 2014: 7914 in April-June 2014, 30 537 in 2015, 75 166 in 2016, and 201 398 in 2017. The percentage of registered users in each province varies, ranging from 0.07% of the Quebec population to 1.7% of the Alberta population. Medical cannabinoids, here defined as medical marijuana and pharmaceutical cannabinoids, have been endorsed for a long list of medical concerns and ailments, from irritable bowel syndrome to cancer. However, enthusiasm among prescribers is inconsistent. Two Canadian surveys have shown that prescribers would appreciate more education and guidance around prescribing of medical cannabinoids.

Although cannabinoids have been promoted for a wide array of medical conditions, the evidence base is challenged by bias and a lack of high-level research. Two large evidence synopses suggested that only three conditions have an adequate volume of evidence: chronic pain, nausea/vomiting, and spasticity. Therefore, this Clinical Practice Guideline Evidence Review Committee performed a targeted systematic review of systematic reviews on the use of cannabinoids for these conditions, as well as their potential adverse effects. Medical cannabinoids included pharmaceutically-derived cannabinoids (nabilone and nabiximols) and medical marijuana. The clinical questions focused on medical cannabinoids as therapy; therefore, we selected systematic reviews that included randomized controlled trials (RCTs) to focus on the highest-level evidence. This systematic review, including GRADE evaluation, is published in full as a companion document to this guideline.

GUIDELINE DEVELOPMENT METHODOLOGY

Following the completion of the systematic review, the guideline began by forming the overarching 10-member Prescribing Guideline Committee (PGC), which consisted of: two general family physicians, one inner city family physician, two pain management-focused family physicians, one neurologist, one medical oncologist, one nurse practitioner, one pharmacist, and one patient representative. There were originally 11 members (two patient members), but one patient representative withdrew due to unavoidable external commitments. There were also two non-voting members to help guide the process (pharmacist project managers). The PGC was responsible for: considering the evidence, discussing application to primary care, developing and approving recommendations from primary care clinicians, assisting in drafting and preparing the guideline, and approving related knowledge translation content. PGC member selections were based on profession, practice setting, and location to represent a variety of primary care providers from across the country, as well as the absence of financial conflicts of interest. Guideline authors and their actual and potential conflicts of interest were disclosed and are available in Appendix D. This guideline received no external funding and no members of the PGC have a financial conflict of interest.

As with a previous guideline, the PGC endeavoured to create a guideline that was evidence-based, primary care-focused, patient-centred and, wherever possible, simplified. The Institute of Medicine’s outline for Clinical Practice Guidelines We Can Trust and GRADE methodology was followed. The guideline development itself was iterative and completed through online communication and telephone meetings.

As previously mentioned, the process started with identification of three possible areas of reasonable evidence for medical cannabinoids and the potential harms. The evidence team then performed a detailed systematic review of systematic reviews (of RCTs) in the following areas:
1. Medical cannabinoids for the management of pain
2. Medical cannabinoids for the management of nausea/vomiting
3. Medical cannabinoids for the management of spasticity
4. Adverse events resulting from medical cannabinoids

PGC members reviewed the results of the systematic reviews and completed pre-meeting work to formulate thoughts around key recommendations for primary care. Medical cannabinoids included pharmaceutically derived cannabinoids (e.g., nabilone and nabiximols) and medical marijuana. At meetings, evidence and application were discussed and the PGC began to compose key recommendations. Recommendations were further drafted between meetings, shared ahead, and then discussed at subsequent meetings. During this process, the PGC had seven additional questions they requested clarification on from the Evidence Review Committee, including:

1. What is the evidence on medical cannabinoids for appetite stimulation?
2. Do cannabinoids reduce seizure frequency in patients with epilepsy?
3. Can cannabinoids be used to treat headaches?
4. Have there been any cases of pulmonary aspergillosis and, if so, was the cannabis smoked or vaporized?
5. What is the efficacy of oral cannabinoids in chronic pain?
6. Is there high-level evidence that differing proportions of THC or CBD influence effectiveness (or harms)?
7. How do cannabinoids compare to other drug treatments for neuropathic pain?

All seven questions were answered using an abbreviated focused search and summation of the best available evidence available in an online supplement. (See Cannabinoid Prescribing Information 2018.)

The principles of GRADE methodology were originally used for wording of recommendations.14 Weak recommendations were represented by the wording “could consider” (in this publication- “consider” terminology was used). Strong recommendations were represented by the wording “we recommend” (in this publication - “DO or DO NOT DO” terminology was used. Four PGC members then completed the first draft of the guideline, which was then distributed to the full PGC for consideration and suggestions. The PGC then met again to finalize the recommendations and document.

The guideline was given to the Peer Review Committee for distribution to outside clinicians and patients for peer review and feedback. The Peer Review Committee compiled feedback from 40 individuals and made suggestions to improve the guideline. Once edited, the guideline was sent to the PGC for final approval. After final approval of the guideline by the PGC, knowledge translation tools, including patient education content, were developed.

**Evidence Limitations**

The focus was on the best available evidence for the review. RCTs and systematic reviews/meta-analyses offer the best possibility of addressing therapy questions, central to prescribing
therapeutics. However, when examining cannabinoids, even this higher-level evidence is subject to multiple and highly impactful biases, considerably influencing the GRADE evaluation. These are reviewed in detail in the systematic review but the primary issues are summarized here.

Many studies enrolled patients with a history of cannabinoid use. This might exaggerate the benefit of interventions and almost certainly minimizes adverse events. In fact, one systematic review found that rare serious adverse events, like psychosis, occurred predominantly among cannabinoid-naïve participants. Blinding was examined in some of the RCTs, asking patients and caregivers if they could identify when cannabinoids or placebos were being used. In all studies reporting on the issue, unblinding was very common (~90%) for both patients and caregivers, regardless of cannabinoid type and/or dose. RCTs with small sample sizes and short duration periods, with an increased potential of falsely positive results, are common in cannabinoid research. A sensitivity analysis on chronic pain RCTs found that smaller and shorter duration RCTs were positive, while larger and longer RCTs found no effect. Other risk of bias issues for RCTs include missing quality markers, like allocation concealment. Risk of bias issues for systematic reviews include inconsistent inclusion of RCTs and inconsistent outcome reporting.

**Shared Informed Decision-Making**

In addition to recommendations, this guideline provides details that promote shared decision making with patients. The recommendations are also reflected in the simplified algorithm (Figure 1) found in Appendix A.

Table 2 outlines the benefits for specific indications, including natural frequencies (event rates) and numbers needed to treat (with duration).
Table 2: Medical cannabinoids estimated benefit when treating chronic pain, chemotherapy-induced nausea and vomiting, or spasticity with GRADE rating of evidence.*

<table>
<thead>
<tr>
<th></th>
<th>Cannabinoids</th>
<th>Control (Placebo unless indicated)</th>
<th>NNT (Number Needed to Treat)</th>
<th>GRADE quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chronic Pain (median follow-up 4 weeks)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥30% Reduction in Chronic (Neuropathic plus Cancer) Pain††</td>
<td>39%</td>
<td>30%</td>
<td>11</td>
<td>Very low</td>
</tr>
<tr>
<td>≥30% Reduction in Neuropathic Pain</td>
<td>38%</td>
<td>30%</td>
<td>14</td>
<td>Very low</td>
</tr>
<tr>
<td>≥30% Reduction in Palliative Pain</td>
<td>30%</td>
<td>23%</td>
<td>Not statistically significant (~15)**</td>
<td>Very low</td>
</tr>
<tr>
<td>Change in Chronic Pain Scales (0-10)†</td>
<td>Baseline ~6 Decreased 1.2-1.6</td>
<td>Baseline ~6 Decreased 0.8</td>
<td>-</td>
<td>Very low</td>
</tr>
<tr>
<td><strong>Chemotherapy-Induced Nausea &amp; Vomiting (median follow-up 1 day)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control of Nausea and Vomiting (Cannabinoids vs. Placebo)</td>
<td>47%</td>
<td>13%</td>
<td>3</td>
<td>Moderate</td>
</tr>
<tr>
<td>Control of Nausea and Vomiting (Cannabinoids vs. Neuroleptics)</td>
<td>31%</td>
<td>16% (versus neuroleptics)</td>
<td>7</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Spasticity (median follow-up 6 weeks)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global Impression of Change</td>
<td>50%</td>
<td>35%</td>
<td>7</td>
<td>Low</td>
</tr>
<tr>
<td>≥30% Improvement in Spasticity</td>
<td>35%</td>
<td>25%</td>
<td>10</td>
<td>Low</td>
</tr>
<tr>
<td>Change in Spasticity (0-10)†</td>
<td>Baseline ~ 6.2 Decreased 1.3-1.7</td>
<td>Baseline ~ 6.2 Decreased 1.0</td>
<td>-</td>
<td>Very low</td>
</tr>
</tbody>
</table>

*From systemic review12
†Scales are Visual Analogue Scale or Numeric Rating Scale with higher scores indicating worse pain or spasticity. Changes with cannabinoids given as range based on varying results.
††Meta-analyzed result included 13 studies on neuropathic pain and 2 studies on cancer pain.
**Confidence intervals suggest that benefit is likely (Risk Ratio 1.34, 95% Confidence Intervals 0.96-1.86), so estimated Number Needed to Treat provided.

Table 3 outlines common adverse events in both natural frequency (i.e., event rates) and numbers needed to harm.
Table 3: Adverse events and estimated event rates for medical cannabinoids, with GRADE of evidence rated High.* Grouping of adverse events follows combinations used in the original research.†

<table>
<thead>
<tr>
<th>TYPE OF ADVERSE EVENT</th>
<th>CANNABINOID EVENT RATE</th>
<th>PLACEBO EVENT RATE</th>
<th>NUMBER NEEDED TO HARM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>81%</td>
<td>62%</td>
<td>6</td>
</tr>
<tr>
<td>Withdrawal due to Adverse Events</td>
<td>11%</td>
<td>~3%</td>
<td>14</td>
</tr>
<tr>
<td>Serious Adverse Events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central Nervous System Effects</td>
<td>60%</td>
<td>27%</td>
<td>4</td>
</tr>
<tr>
<td>“Feeling High”</td>
<td>35%</td>
<td>3%</td>
<td>4</td>
</tr>
<tr>
<td>Sedation</td>
<td>50%</td>
<td>30%</td>
<td>5</td>
</tr>
<tr>
<td>Speech Disorders</td>
<td>32%</td>
<td>7%</td>
<td>5</td>
</tr>
<tr>
<td>Dizziness</td>
<td>32%</td>
<td>11%</td>
<td>5</td>
</tr>
<tr>
<td>Ataxia/Muscle Twitching</td>
<td>30%</td>
<td>11%</td>
<td>6</td>
</tr>
<tr>
<td>Numbness</td>
<td>21%</td>
<td>4%</td>
<td>6</td>
</tr>
<tr>
<td>Disturbance Attention/Disconnected Thought</td>
<td>17%</td>
<td>2%</td>
<td>7</td>
</tr>
<tr>
<td>Hypotension</td>
<td>25%</td>
<td>11%</td>
<td>8</td>
</tr>
<tr>
<td>Dysphoria</td>
<td>13%</td>
<td>0.3%</td>
<td>8</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>17%</td>
<td>5%</td>
<td>9</td>
</tr>
<tr>
<td>Euphoria</td>
<td>15%</td>
<td>2%</td>
<td>9</td>
</tr>
<tr>
<td>Impaired Memory</td>
<td>11%</td>
<td>2%</td>
<td>12†</td>
</tr>
<tr>
<td>Disorientation/Confusion</td>
<td>9%</td>
<td>2%</td>
<td>15</td>
</tr>
<tr>
<td>Blurred Vision/Visual Hallucination</td>
<td>6%</td>
<td>0%</td>
<td>17</td>
</tr>
<tr>
<td>Diss (ref15) examples of harms selected from largest statistically significant meta – analyses, providing event rates. Disorientation/Acute Psychosis</td>
<td>5%</td>
<td>0%</td>
<td>20</td>
</tr>
</tbody>
</table>

*From systematic review† examples of harms selected from largest statistically significant meta-analyses providing event rates.
†Confidence intervals suggest that harm is likely (Risk Ratio 3.41, 95% Confidence Intervals 0.95-12.27), so estimated Number Needed to Harm provided.

Figure 2 (see Appendix B) provides a comparison icon-array with natural frequencies for common interventions for neuropathic pain. This tool is not meant to recommend specific therapies, but to allow clinicians and patients to see the estimated benefits of varying interventions. Adverse events, costs and patients’ preferences are some of the issues that also contribute to medication selection. For example, while high-dose opioids have benefits similar to venlafaxine or pregabalin, the risks and harms of high-dose opioids make them a poor choice. A guideline summary is provided with key messages of the guideline and shared-decision making information.
A pamphlet for patients is also provided (see Appendix C).

CANNABINOIDS FOR MOST MEDICAL CONDITIONS

Although advocated for a wide variety of medical conditions, the evidence for medical cannabinoids for most conditions is sparse. This guideline will deal specifically with pain, nausea/vomiting, and spasticity, as these conditions have both the greatest volume of evidence and research that supports a potential benefit. There is insufficient evidence, evidence indicating a lack of benefits, or both for most other conditions. For example, the evidence for glaucoma consists of one RCT of six patients that found no benefit. Even in areas with more research, such as appetite stimulation, RCT results are generally inconsistent and the results are frequently insignificant (Cannabinoid Prescribing Information 2018). For example, of four appetite stimulation RCTs in HIV, two found no difference versus placebo, one found ~2kg improvement with cannabinoids versus placebo, and one found megestrol improved weight 8.5kg more than cannabinoids. For seizure disorders, a Cochrane systematic review reported four low-quality RCTs with 9-15 patients each, and did not find that there was any reliable information to support cannabinoids for seizure prevention (Cannabinoid Prescribing Information 2018). Since then, a 2017 high-quality RCT of cannabidiol for treatment-resistant seizures in Dravet syndrome (aged 2-18 years) showed some improvement in the seizures. While positive, this type of condition would not be managed in primary care and is therefore not relevant to a primary care guideline.

While mental health is a common reason for medical marijuana use, the evidence is very poor. There are no RCTs investigating medical cannabinoids for depression. The evidence for anxiety consists of one RCT of 24 patients who performed a simulated public speaking activity and then reported improvement on the mood visual analogue scale. The evidence for post-traumatic stress disorder (PTSD) consists of one RCT of 10 patients which found benefit in some outcomes but these results disagree with other research findings of marijuana use worsening of PTSD. Overall, the present evidence for medical cannabinoids is insufficient to support use in mental health.

The PGC recommends against the use of cannabinoids for most medical conditions, mostly due to the known harms weighed against the lack of supporting evidence for benefit.

PAIN

There was insufficient evidence for most subtypes of pain. For acute pain, one systematic review of seven RCTs demonstrated that cannabinoids have no reliable effect compared to placebo. For headaches, only one small, flawed crossover RCT was identified (Cannabinoid Prescribing Information 2018), meaning there was insufficient evidence to recommend cannabinoids for headache. For pain associated with rheumatologic conditions, three systematic reviews reported insufficient evidence for benefit in fibromyalgia, osteoarthritis, rheumatoid arthritis and back pain. Given these findings, and the high risk of harms, the PGC recommends against cannabinoids for these conditions.
NEUROPATHIC PAIN

Cannabinoid use increased the number of patients who achieve a 30% pain reduction in chronic (13 neuropathic and two cancer RCTs), with a risk ratio of 1.37 (95% CI, 1.14 to 1.64).\(^1\) Looking specifically at neuropathic pain, in the largest meta-analysis (nine RCTs) cannabinoid use increased the number of patients who achieve a 30% pain reduction, with a risk ratio of 1.34 (95% CI, 1.04 to 1.74). Given that the chronic pain meta-analyses were larger (specifically, ≥10 RCTs), we performed sensitivity analyses on this group of studies and demonstrated that longer or larger RCTs found no effect in chronic pain.\(^1\) This raises considerable uncertainty regarding cannabinoids’ true effect on chronic pain. Additionally, even if we assume estimated benefits are real, many of the adverse events are more common than the benefits. Weighing this information, and the fact that many other agents are more effective with fewer harms, the PGC felt that clinicians should only consider cannabinoids after three or more established agents for neuropathic pain have had a reasonable therapeutic trial.

It is also important to note that the majority of pain studies used cannabinoids with concomitant analgesia.\(^1\) Therefore, if cannabinoids are used, it should be as adjuncts to other analgesics. Other research shows almost half of patients with neuropathic pain will require at least two agents.\(^1\) Although HIV-related neuropathy is often unresponsive to other analgesics, the evidence for cannabinoids for this indication is highly biased and unreliable. For example, two studies in HIV neuropathic pain were both short (<2 weeks) and small (34 and 55 patients).\(^1\) Therefore, the PGC was not able to provide a specific recommendation for this indication beyond that for general neuropathic pain.

CANCER/PALLIATIVE PAIN

The research for medical cannabinoids in cancer/palliative pain is not as robust as for neuropathic pain. However, the PGC considered the potential, although not reliably verified, for concurrent small benefits for nausea/vomiting and appetite stimulation (Cannabinoid Prescribing Information 2018), as well as the reduced concern about long-term adverse effects in this population. This led to a weak recommendation for considering use in refractory cancer/palliative pain. Weighing these deliberations with the reality that the management of cancer/palliative pain progresses more rapidly to opioid analgesia compared to other chronic pain conditions, the PGC felt that clinicians should only consider cannabinoids after two or more established agents for cancer/palliative pain have had a reasonable therapeutic trial.\(^1\)

NAUSEA AND VOMITING

Due to the absence of evidence and known harms of medical cannabinoids, the PGC recommends against cannabinoids for general nausea/vomiting. Due to the additional unknown harms to the unborn fetus caused by medical cannabinoids in pregnancy-induced nausea/vomiting or hyperemesis gravidarum, the recommendation against cannabinoid use for these conditions was strengthened.
CHEMOTHERAPY-INDUCED NAUSEA/VOMITING (CINV)

CINV remains a common consequence of cancer treatment. Meta-analysis (seven RCTs) shows that medical cannabinoids (nabilone or dronabinol) help more patients avoid CINV, with a risk ratio or 3.60 (95% CI, 2.55 to 5.09). However, four of the seven RCTs were ≥35 years old and would not have included therapies in current use. Furthermore, many RCTs followed patients for only one day. Current recommended treatments of CINV depend on the emetogenicity of the selected chemotherapy protocol and classification of the symptoms (acute onset, delayed onset, anticipatory). Contemporary recommended treatments for CINV often include ondansetron, dexamethasone, and aprepitant, with metoclopramide prescribed as needed. Weighing these considerations, the PGC felt medical cannabinoids could only be considered for CINV refractory to current antiemetic therapies.

SPASTICITY

Due to the limited evidence for use in spasticity (other than in multiple sclerosis or spinal cord injury) and the known harms of medical cannabinoids, the PGC recommended against the use of medical cannabinoids for general spasticity.

SPASTICITY IN MULTIPLE SCLEROSIS (MS) AND SPINAL CORD INJURY (SCI)

Spasticity is a common symptom in MS and SCI. In MS, meta-analysis (three RCTs) shows that medical cannabinoids (nabiximols) increased the number of patients achieving a 30% improvement in spasticity, with a risk ratio of 1.37 (95% CI, 1.07 to 1.76). Although the number of RCTs in SCI is far less (three versus 11 for MS), the trials generally show similar results. However, the PGC recognized that there are a number of established therapies for spasticity (for example). Furthermore, nabiximols are very expensive and, as with all medical cannabinoids, adverse events are more common than benefits. Therefore, the PGC felt medical cannabinoids could only be considered for MS or SCI spasticity refractory to current established therapies. Lastly, the PGC felt it was important to differentiate spasticity from spasms, as the recommendation does not apply to spasms.

HARMS OF CANNABINOIDS

Harms of cannabinoids were consistent and common across all prescribing considerations. Furthermore, harms were consistent within research trials and represent the highest level of GRADE evidence within the systematic review. Table 3 provides a list of adverse events. GRADE evaluation of evidence started as high (from meta-analyses of RCTs) but was decreased due to risk of bias and imprecision. However, GRADE was also increased for large magnitudes of effect and confounders that would decrease adverse events (like selective inclusion of past cannabinoid users). This meant the final evidence GRADE for adverse events was high.

Across studies, the approximate risk of adverse events is 80% versus 60%, and withdrawal due to adverse events is 11% versus 3% for cannabinoids and placebo, respectively. The overall risk of adverse events is similar among varying types of medical cannabinoids (such as nabiximols or...
Certain adverse events, like “feeling high” (35-70% versus 0-3%) and euphoria (15% versus 2%), are very common, but likely anticipated. Other common adverse events, which were potentially less desirable and more relevant to the committee, include sedation (50% versus 30%), dysphoria (13% versus 1%), disorientation/confusion (9% versus 2%), disturbed attention/disconnected thoughts (17% versus 2%), dizziness (32% versus 11%), and hypotension (25% versus 11%).

Long-term and serious adverse events are underestimated in our systematic review due to our focused use of meta-analyses of RCTs. This is exacerbated by enrolment of previous cannabinoid users in the RCTs and the predominance of small RCTs with short durations. As a result, the risk of psychosis appears to be underestimated. The risks of rare events, such as cannabinoid hyperemesis syndrome (cyclic vomiting) and amotivational syndrome, are still being defined.

Cannabis use disorder (CUD), replacing previous cannabis abuse and cannabis dependence, may be as common as one fifth of regular cannabis users. Risk of CUD is higher in those who use more frequently, are male, and begin earlier. However, in another study of those meeting criteria for having CUD, 67% remitted (no longer met criteria) at three years, with 64% of them no longer using cannabis. Whether regular medical use may result in CUD, what outcomes this may have, and if discontinuation presents concerns are all not well understood.

**PRESCRIBING CONSIDERATIONS**

**PHARMACEUTICAL CANNABINOIDs (NABILONE AND NABIXIMOLS)**

Prescribing for CINV should focus on nabilone, and nabiximols for spasticity in MS or SCI, based on the evidence and marketing authority in Canada. The PGC recognized that nabilone, an oral synthetic cannabinoid, is used off-label for pain and has limited evidence of benefit. However, it is relatively inexpensive, is covered by many public drug plans, and can be dosed more consistently due to its capsule formulation. Nabiximols is a combination of THC/CBD available as an oromucosal spray. It is expensive, rarely covered on public drug plans, and has limitations to prescribing in some Canadian provinces. However, nabiximols has better evidence for spasticity and neuropathic pain.

**SMOKED AND OTHER MEDICAL MARIJUANA**

The PGC recognizes that when patients request medical cannabinoids they are likely considering smoked and other medical marijuana formulations. Reasons for this include symptom improvement with previous cannabis experience, secondary gain related to known cannabinoid effects, patients’ desire to use a natural product, information from media/internet/personal contacts, or unawareness of other formulations available. Regardless, there are a number of important considerations here. First, the literature around smoked medical marijuana demonstrates a significant risk of bias, including possibly exaggerated benefits and underreported harms. Second, the long-term harms (including smoking) and serious adverse effects would not be adequately captured in RCTs and so are largely unknown. Third, dosing with medical marijuana poses an issue as THC/CBD concentrations vary considerably with differing medical marijuana products. In fact, many dried medical marijuana products have THC concentrations of ≥15% while the highest studied is only 9.4%. Additionally, mode of delivery and/or volume per use can substantially change total intake.
There is no evidence that the different formulations of medical marijuana, such as cannabis oil, are more effective or safer than dried medical marijuana. Lastly, cases of pulmonary aspergillosis have been reported in immunocompromised patients. (See Cannabinoid Prescribing Information 2018.)

Medical recommendations in the literature are often for small amounts of lower potency marijuana. For example, the starting recommended dosing is one inhalation of a 9% maximum THC “joint” once per day. This can be increased to one inhalation four times a day, resulting in approximately half a “joint” per day (or 400mg). People should not operate dangerous equipment or perform potentially dangerous activities after use. This includes no driving for three to four hours after inhaled medical marijuana, six hours after oral medical marijuana, and eight hours if a “high” was noted. For further specific recommendations, monitoring, and guidance regarding prescribing medical marijuana, we suggest the guidance document by Kahan et al 2014. There are also many national and provincial associations/colleges/governmental groups that provide policy and guidance for prescribers. (See Cannabinoid Prescribing Information 2018.) We provide a summary of the provincial guidance within the online supplement. We also provide a list of authorized licensed producers of medical marijuana. (See Cannabinoid Prescribing Information 2018.) Note: licensed providers often do not involve authorizing clinicians in the titration of medical marijuana and may simply allow patients to select medical marijuana types. It should be clear that if patients use 5 grams (current maximum) of 15% THC, this represents approximately 20 times higher dosing than the recommended 400mg of 9% THC.

At the time of writing, prices from licenced producers (online supplement) ranged from $4.25 to $15 per gram. Public Safety Canada reported the mean price from licenced producers was $8.37 (standard deviation $2.34) per gram. Given most patients smoke 1-3 grams per day (compared to the recommend 400mg per day), typical costs would be approximately $250-750/month.

We have indicated authorized licensed providers that provide space for clinician recommendations. (See Cannabinoid Prescribing Information 2018.) Lastly, it should be noted that in whatever form cannabinoids are taken, they can have interactions with other pharmaceuticals, with particular concerns about increase central nervous system effects.

CONCLUSION

Medical cannabinoids challenge clinicians, particularly as we attempt to provide symptom and functional improvement in patients that are refractory to other therapies. The evidence for medical cannabinoids is unfortunately sparse in many areas and very frequently downgraded by serious bias, limiting the ability to provide clear guidance. Overall, the PGC felt that medical cannabinoids are not recommended for the vast majority of patients and conditions. In neuropathic pain, palliative cancer pain, CINV, and MS/SCI-related spasticity, they should only be considered for patients refractory to standard medical therapies. When considered, there should be a discussion with patients regarding the limited benefits, more common harms, and a preferential trial of pharmaceutical cannabinoids first (over medical marijuana). We hope that future high quality RCTs will clarify the evidence further and may lead to re-evaluation of the recommendations. We also recommend long-term monitoring of medical cannabinoid to further assess potential individual and societal benefits/harms.
REFERENCES


**SUGGESTED CITATION**


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January 2018
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**Clinical Practice Guideline**

**Appendix A**

**Figure 1: Medical cannabinoid prescribing algorithm**

- If Considering Medical Cannabinoids
  - For: Neuropathic Pain, Palliative Pain, Spasticity in Multiple Sclerosis (MS) or Spinal Cord Injury (SCI), Chemotherapy-induced Nausea/Vomiting (CINV)
  - If tried: ≥3 medications for neuropathic pain or ≥2 medications for palliative pain; or if refractory to standard therapies for CINV or spasticity in MS or SCI
  - May consider a medical cannabinoid as adjunctive therapy:
    - Neuropathic or Palliative Pain: Try nabilone or nabiximols
    - Chemotherapy-induced Nausea/Vomiting: Try nabilone
    - Spasticity in MS or SCI: Try nabilone or nabiximols

We recommend **against prescribing medical marijuana (particularly smoked) as a first-line cannabinoid** due to a high risk of bias in available studies and unknown long-term consequences. In all cases, potential harms and benefits should be discussed with the patient.
### Appendix B

**Figure 2: Neuropathic Pain: Pharmacotherapy Treatment**

**Outcome:** Meaningful (~30%) Pain Improvement

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<thead>
<tr>
<th>Medication</th>
<th>Number with Treatment</th>
<th>Number with Placebo or No Treatment</th>
<th>Number with No Improvement</th>
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<td><strong>Amitriptyline</strong></td>
<td>25</td>
<td>25</td>
<td>50</td>
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<td><strong>Venlafaxine</strong></td>
<td>17</td>
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<td><strong>Pregabalin</strong></td>
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<td><strong>Gabapentin</strong></td>
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<td>25</td>
<td>60</td>
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<td><strong>Duloxetine</strong></td>
<td>13</td>
<td>25</td>
<td>62</td>
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<td><strong>Cannabinoids</strong></td>
<td>9</td>
<td>25</td>
<td>66</td>
</tr>
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**High Dose Opioids**

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<tr>
<td>18</td>
<td>Improve with treatment</td>
</tr>
<tr>
<td>25</td>
<td>Improve with placebo or no treatment</td>
</tr>
<tr>
<td>57</td>
<td>No improvement</td>
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*50-110mg oral morphine per day

**Limitations**
1. Based on indirect comparisons.
2. Timeframe ~4 to 12 weeks.
3. Details on methods available in online supplement.

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APPENDIX C

PATIENT BROCHURE

Medical Cannabinoids

There are a lot reasons people might ask their health care provider about medical cannabinoids or medical marijuana. You may have heard that it can help with some health problems.

Maybe you are interested because it is natural. Or maybe you have tried it in the past and found it helpful.

What are medical cannabinoids?
The word “cannabinoids” can mean two things: marijuana (dried plant or oils) and manufactured products (sprays or pills). Some people use cannabinoids recreationally and some people use them to treat health problems.

Manufactured Cannabinoids
- capsules
- spray

Medical Marijuana
- dried marijuana
- marijuana oils

= Medical Cannabinoids

There are a lot options when treating health problems. It is suggested that you try some standard treatments before thinking about medical cannabinoids.

Will medical cannabinoids work for me?
There’s not a lot of high quality research on medical cannabinoids. But based on the best research, cannabinoids may help people with:
- Nerve pain
- End-of-life pain
- Nausea and vomiting caused by chemotherapy
- Muscle spasticity caused by multiple sclerosis (MS) or spinal cord injury

What percentage of patients will get better?

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<tr>
<th>Benefit</th>
<th>With Placebo</th>
<th>With Cannabinoids</th>
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<tr>
<td>Reduce nerve pain</td>
<td>50%</td>
<td>58%</td>
</tr>
<tr>
<td>Reduce end-of-life pain</td>
<td>29%</td>
<td>60%</td>
</tr>
<tr>
<td>Reduce nausea and vomiting caused by chemotherapy</td>
<td>13%</td>
<td>47%</td>
</tr>
<tr>
<td>Reduce spasticity caused by MS or spinal cord injury</td>
<td>25%</td>
<td>35%</td>
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For more information please go to: www.pain-calculator.com

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### Common side effects

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<th>With Cannabinoids</th>
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<td>Low blood pressure</td>
<td>11%</td>
<td>25%</td>
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<tr>
<td>Dizziness</td>
<td>11%</td>
<td>32%</td>
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<td>Memory problems</td>
<td>2%</td>
<td>11%</td>
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<tr>
<td>Feeling sleepy</td>
<td>30%</td>
<td>50%</td>
</tr>
<tr>
<td>Feeling ‘high’</td>
<td>3%</td>
<td>35%</td>
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<tr>
<td>Muscle twitching</td>
<td>11%</td>
<td>30%</td>
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<td>Feeling unhappy</td>
<td>Less than 1%</td>
<td>13%</td>
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<tr>
<td>Numbness</td>
<td>4%</td>
<td>21%</td>
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<tr>
<td>Feeling disconnected from reality</td>
<td>0%</td>
<td>5%</td>
</tr>
<tr>
<td>Trouble speaking</td>
<td>7%</td>
<td>32%</td>
</tr>
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**Why might my health care provider say “no” to cannabinoids?**
- Overall the research is poor
- For most health problems, there’s not enough research to tell if they work
- Side-effects are common
- Long-term harms are unknown

**Why is my health care provider suggesting manufactured cannabinoids instead of marijuana?**
Manufactured products (sprays or pills) are like marijuana but have been studied more. Doses can be controlled better. Also, some of the manufactured products might be covered by your drug plan.

### Things to consider

If you are thinking about using medical cannabinoids, smoked marijuana is not recommended. Smoking may cause other harms.

### Start the conversation

Some people worry that their health care provider does not want to talk about cannabinoids. Talking about cannabinoids is important. Your health care provider can work with you because cannabinoids may:
- Affect your medications
- Cause side effects
- Be expensive
- Improve your symptoms, leading to a change in other medication

**You should always talk to your health care provider before starting or changing treatment.**
## APPENDIX D

### Medical Cannabinoids in Primary Care Prescribing Guideline Contributors Disclosed Conflicts of Interest

<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
<th>Written articles*</th>
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<tr>
<td>G. Michael Allan</td>
<td>Professor and Director of EBM, Dept of Family Medicine, U of A. Director of Evidence and CPD, Alberta College of Family Physicians</td>
<td>Written “Tools for Practice”, editorials and research articles</td>
<td>On evidence surrounding cannabinoid use for medical conditions in Canada</td>
<td>No, but will be working on one</td>
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<td>Xiaofu Zhu</td>
<td>Medical Oncologist, Cross Cancer Institute</td>
<td>X</td>
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<tr>
<td>Ted Findlay</td>
<td>Consultant, AHS Chronic Pain Centre, Clinical Assistant Professor, University of Calgary</td>
<td>X</td>
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<tr>
<td>Ruth Dubin</td>
<td>Assistant Professor, Queens University and Northern Ontario School of Medicine</td>
<td>Worked on CFPC preliminary guidance document</td>
<td>Presented on risks, harms and benefits of cannabinoids to CFPC, ECHO Ontario</td>
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<tr>
<td>Nicole Crisp</td>
<td>NP-Adult, Division of Hematology, University of Alberta Hospital</td>
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<td>X</td>
<td>X</td>
<td>Sub-investigator on clinical trials for MDS/AML with Pfizer, Merck, Novartis, Celgene, and Daiichi Sankyo</td>
</tr>
<tr>
<td>Nathan Beahm</td>
<td>Research Fellow, EPICORE Centre, University of Alberta</td>
<td>Tools for Practice on medical cannabinoids for pain</td>
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<tr>
<td>Michael Fleming</td>
<td>Family Practice &amp; Director of Family Physician Programs in CPD, Dalhousie University Faculty of Medicine</td>
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<td>Ken Makus</td>
<td>Director, Adult Convulsive Disorder Clinic, Clinical Assistant Professor, University of Alberta</td>
<td>X</td>
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<td>Jessica Kirkwood</td>
<td>Family physician, Boyle McCauley Health Centre</td>
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<tr>
<td>Bev Dockrill</td>
<td>Patient representative, retired RN</td>
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<td>Adrienne J Lindblad</td>
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<td>Christina Korownyk</td>
<td>Associate Professor, Evidence-Based Medicine, Dept of Family Medicine University of Alberta</td>
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<td>Sharon Nickel</td>
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<tr>
<td>Jamil Ramji</td>
<td>Knowledge Translation Expert, Evidence-Based Medicine, Department of Family Medicine</td>
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*Please note that the table entries are placeholders and do not reflect actual data or affiliations.*
These recommendations are systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances. They should be used as an adjunct to sound clinical decision making.

### Clinical Practice Guideline

#### Appendix D

<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
<th>Written articles*</th>
<th>Presented*</th>
<th>Created apps, software, tools, etc.*</th>
<th>Advisory Board**</th>
<th>Speaker s’ Bureau**</th>
<th>Payment**</th>
<th>Grant(s) or Honorarium **</th>
<th>Patent</th>
<th>Investment s</th>
<th>Clinical Trial</th>
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<tr>
<td>Guillermina Noël</td>
<td>Health Innovation Studio Lead &amp; Human-centred Knowledge Designer, Lifelong Learning, Faculty of Medicine &amp; Dentistry, University of Alberta</td>
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<td>X</td>
<td>Knowledge dissemination tool (CADTH)</td>
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