The Use of Medical Cannabis with Other Medications: A Review of Safety and Guidelines

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Context and Policy Issues

Marijuana or cannabis is a tobacco-like material harvested from the flowers, fruit tops, and leaves of the cannabis plant, *Cannabis sativa*. The plant produces many distinct compounds from different chemical classes, including over 60 cannabinoids. Cannabinoids, such as tetrahydrocannabinol (THC) and cannabidiol (CBD), are active ingredients from cannabis. THC is the primary psychoactive component with analgesic effects, while CBD is a non-psychoactive component with anti-inflammatory, analgesic, and antipsychotic properties. In addition to the cannabis extract, THC and CBD have been synthesized for prescribed medical use, such as dronabinol (i.e., THC only), nabilone (i.e., synthetic derivative mimicking THC) and nabiximols (i.e., THC and CBD). The term “medical cannabis” used in this report refers to both the cannabis plant and its synthetic cannabinoids that are used for medical purposes.

On August 24, 2016, Health Canada announced the *Access to Cannabis for Medical Purposes Regulations*, which allows Canadians to access to a reasonable amount of cannabis for medical purposes prescribed by health care practitioners. Cannabis and cannabinoids may be used for medicinal purposes for the treatment of an array of symptoms in patients, who have not responded to conventional therapies. They include nausea and vomiting associated with cancer chemotherapy, loss of appetite in HIV/AIDS and cancer patients, pain and spasticity due to multiple sclerosis, chronic non-cancer pain, cancer pain, symptoms in the palliative care setting, insomnia and depression.

Both THC and CBD are metabolized by the drug metabolizing enzymes of the cytochrome P450 (CYP-450) system. The CYP1A2, CYP2C9 and CYP3A4 enzymes are responsible for the metabolism of numerous prescribed medications as well as exogenous cannabinoids. In vitro and ex vivo studies have shown that exogenous cannabinoids may act as substrates, inhibitors or inducers of various CYP-450 isoforms. Thus, adverse effects from drug-drug interactions may occur when patients are treated with medical cannabis concomitantly with other medications.

The aim of this report is to review the clinical evidence and evidence-based guidelines regarding the safety and interaction of the use of medical cannabis with other medications.

**Research Questions**

1. What is the clinical evidence regarding the safety of the use of medical cannabis with other medications?

2. What are the evidence-based guidelines regarding the interaction of the use of medical cannabis with other medications?
Key Findings
Limited data on medical cannabis and drug-drug interactions were obtained from a low quality systematic review. Nabilone may have additive depressant effects with diazepam when taken together with alcohol and codeine, and it may decrease the need for opioids, nonsteroidal anti-inflammatory drugs, tricyclic antidepressants, dexamethasone and ondansetron when used concomitantly. No evidence-based guidelines were identified.

Methods
Literature Search Methods
A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2012 and March 24, 2017.

Selection Criteria and Methods
One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

<table>
<thead>
<tr>
<th>Population</th>
<th>Any patient taking cannabis to treat a medical condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Q1: Medical cannabis with other medications</td>
</tr>
<tr>
<td></td>
<td>Q2: Recommendations on the use of medical cannabis interacting with other medications (including dosage)</td>
</tr>
<tr>
<td>Comparator</td>
<td>Q1: Other medications, including illicit substances and alcohol</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Q2: No comparator</td>
</tr>
<tr>
<td></td>
<td>Q1: Drug-drug interactions, safety, harms</td>
</tr>
<tr>
<td></td>
<td>Q2: Guidelines</td>
</tr>
<tr>
<td>Study Designs</td>
<td>Health technology assessments (HTAs), systematic reviews (SRs), meta-analyses (MAs), randomized controlled trials (RCTs), non-randomized studies, evidence-based guidelines</td>
</tr>
</tbody>
</table>

Exclusion Criteria
Studies were excluded if they did not satisfy the selection criteria in Table 1, and if they were published prior to 2012. Conference abstracts, duplicates of publication of the same study were excluded.

Critical Appraisal of Individual Studies
The SIGN checklist was used to assess the quality of systematic reviews (SRs).9
Summary of Evidence

Quantity of Research Available
A total of 284 citations were identified in the literature search. Following screening of titles and abstracts, 267 citations were excluded and 17 potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 16 publications were excluded for various reasons, while one systematic review (SR) met the inclusion criteria and was included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics
The characteristics of the SR\textsuperscript{10} are summarized below and presented in Appendix 2.

\textit{Study Design}
The SR\textsuperscript{10} included 11 primary studies (i.e., eight RCTs, two prospective cohort studies, and one retrospective chart review) related to nabilone for the management of pain.

\textit{Country of Origin}
The SR was from Canada and was published in 2016.\textsuperscript{10}

\textit{Population}
The included patients (N=655) were between 23 to 84 years old and had various pain conditions, including cancer pain, chronic non-cancer pain, neuropathic pain, fibromyalgia, and pain associated with spasticity.

\textit{Interventions and Comparators}
For the intervention, nabilone was given concomitantly with other medications, such as opioids, non-steroidal anti-inflammatory drugs, tricyclic antidepressants, dexamethasone, ondansetron, and with the combination of diazepam, alcohol and codeine. The comparator was placebo or no nabilone treatment.

\textit{Outcomes}
The outcomes were pain, anxiety, sleep disturbance, and adverse drug reactions, including precautions and contraindications, drug-drug interactions, abuse potential, and dosing.\textsuperscript{10}

\textit{Follow-up Period}
The follow-up period of the included studies was not reported.

\textit{Data Analysis and Synthesis}
The findings of drug-drug interactions were narratively described without providing any data.

\textit{Quality Appraisal}
The quality of the included primary studies was not assessed.
Summary of Critical Appraisal

The quality assessment of the included SR was briefly described below and presented in Appendix 3.

The quality of the included SR\textsuperscript{10} was low. It did not report the number of reviewers involved in the study selection and data extraction, provide an excluded studies list, perform a quality assessment of the included studies, or declare if there were any conflicts of interest. A meta-analysis and an assessment of publication bias were not applicable. The SR was explicit in terms of research question, comprehensive literature search and inclusion criteria.

Summary of Findings

\textit{Question 1: What is the clinical evidence regarding the safety of the use of medical cannabis with other medications?}

The main findings and conclusions of the included SR are presented in Appendix 4.

\textit{Clinical Effects}

When nabilone was combined with diazepam, alcohol and codeine, an additive central nervous system depression was observed. Nabilone had opioid-sparing effects that when it is combined with opioids, the opioid dose can be lowered without compromising the opioid effect. Similarly, nabilone may decrease the need for other medications, such as nonsteroidal anti-inflammatory drugs (NSAIDs), tricyclic antidepressants (TCAs), dexamethasone, and ondansetron in advanced cancer patients.

\textit{Question 2: What are the evidence-based guidelines regarding the interaction of the use of medical cannabis with other medications?}

No evidence-based guidelines were identified.

Limitations

Data on the drug interactions of medical cannabis with other medications were very limited. No primary clinical studies that met the selection criteria of this review were identified. There were also no evidence-based guidelines regarding the use of medical cannabis with other medications. Although one SR met the inclusion criteria, its methodological quality was low, and the findings of drug-drug interactions were from only two studies and were narratively reported without providing any data.

Conclusions and Implications for Decision or Policy Making

Limited data were available on the drug interactions with medical cannabis. Nabilone may have additive depressant effects with diazepam when taken together with alcohol and codeine, and it may decrease the need for opioids, NSAIDs, TCAs, dexamethasone and ondansetron when used concomitantly. The study findings were from a low quality SR, and, therefore, should be interpreted with caution.
References


Appendix 1: Selection of Included Studies

284 citations identified from electronic literature search and screened

267 citations excluded

17 potentially relevant articles retrieved for scrutiny (full text, if available)

0 potentially relevant reports retrieved from other sources (grey literature, hand search)

17 potentially relevant reports

16 reports excluded:
- Reviews (n=6)
- Irrelevant population (n=3)
- Irrelevant study design (n=4)
- Irrelevant intervention or outcomes (n=3)

1 SR included in review
### Appendix 2: Characteristics of Included Studies

#### Table A1: Characteristics of Included Systematic Reviews

<table>
<thead>
<tr>
<th>First Author, Publication Year, Country, Funding</th>
<th>Types and Numbers of Primary Studies Included</th>
<th>Population Characteristics</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Clinical Outcomes, Length of Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tsang and Giudice, 2016&lt;sup&gt;10&lt;/sup&gt; Canada Funding: NR</td>
<td>SR of 8 RCTs, two prospective cohort studies and one retrospective chart review related to nabilone for the management of pain published between 2006 and 2015 Quality assessment of primary studies was not performed</td>
<td>655 patients with pain conditions including cancer pain, chronic non-cancer pain, neuropathic pain, fibromyalgia, and pain associated with spasticity Age: 23 to 84 years Gender: NR</td>
<td>Nabilone</td>
<td>Placebo or no treatment</td>
<td>• Pain • Anxiety and sleep disturbance • Adverse drug reactions including precautions and contraindications, drug interactions, abuse potential • Dosing Follow-up: NR</td>
</tr>
</tbody>
</table>

NR = not reported; RCT = randomized controlled trial; SR = systematic review
Appendix 3: Quality Assessment of Included Studies

Table A2: Quality Assessment of Systematic Reviews

<table>
<thead>
<tr>
<th>SIGN Checklist: Internal Validity</th>
<th>Tsang and Giudice, 2016¹⁰</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The research question is clearly defined and the inclusion/exclusion criteria must be listed in the paper</td>
<td>Yes</td>
</tr>
<tr>
<td>2. A comprehensive literature search is carried out</td>
<td>Yes</td>
</tr>
<tr>
<td>3. At least two people should have selected studies</td>
<td>Not reported</td>
</tr>
<tr>
<td>4. At least two people should have extracted data</td>
<td>Not reported</td>
</tr>
<tr>
<td>5. The status of publication was not used as an inclusion criteria</td>
<td>Yes</td>
</tr>
<tr>
<td>6. The excluded studies are listed</td>
<td>No</td>
</tr>
<tr>
<td>7. The relevant characteristics of the included studies are provided</td>
<td>Yes</td>
</tr>
<tr>
<td>8. The scientific quality of the included studies was assessed and reported</td>
<td>No</td>
</tr>
<tr>
<td>9. Was the scientific quality of the included studies used appropriately?</td>
<td>No</td>
</tr>
<tr>
<td>10. Appropriate methods are used to combine the individual study findings</td>
<td>Not applicable</td>
</tr>
<tr>
<td>11. The likelihood of publication bias was assessed appropriately</td>
<td>Not applicable</td>
</tr>
<tr>
<td>12. Conflicts of interest are declared</td>
<td>No</td>
</tr>
</tbody>
</table>

Overall Assessment of the Study

High, Moderate, Low

Low

For overall assessment of the study: High indicated that all or most criteria have been fulfilled; where they have not been fulfilled, the conclusions of the study or review are thought very unlikely to alter. Moderate indicates that some of the criteria have been fulfilled; those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions. Low indicates that few or no criteria fulfilled; the conclusions of the study are thought likely or very likely to alter.
### Table A3: Summary of Findings of Included Systematic Reviews

<table>
<thead>
<tr>
<th>Main Study Findings</th>
<th>Author’s Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug-drug interactions (from two primary studies)</strong></td>
<td>No conclusion regarding drug-drug interactions</td>
</tr>
<tr>
<td><strong>Medical Cannabis</strong></td>
<td><strong>Concomitant drugs</strong></td>
</tr>
<tr>
<td>Nabilone</td>
<td>Diazepam, alcohol, codeine</td>
</tr>
<tr>
<td>Nabilone</td>
<td>Opioids</td>
</tr>
<tr>
<td>Nabilone</td>
<td>NSAIDs, TCAs, dexamethasone, ondansetron</td>
</tr>
</tbody>
</table>

NSAIDs = non-steroidal anti-inflammatory drugs; TCAs = tricyclic antidepressants
Appendix 5: Additional References of Potential Interest

Systematic review

Marijuana Smoking not used for Medical Purposes

Primary Studies

No Comparator

Case Reports


Patient Population were Healthy Adults


Narrative Reviews


