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CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

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

Service Line:	Rapid Response Service
Version:	1.0
Publication Date:	April 19, 2017
Report Length:	13 Pages

CADTH

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Cite As: The Use of Medical Cannabis with Other Medications: A Review of Safety and Guidelines. Ottawa: CADTH; 2017 April. (CADTH rapid response report: summary with critical appraisal).

Acknowledgments:

ISSN: 1922-8147 (online)

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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*.[1] The plant produces many distinct compounds from different chemical classes, including over 60 cannabinoids.[2] Cannabinoids, such as tetrahydrocannabinol (THC) and cannabidiol (CBD), are active ingredients from cannabis.[2,3] THC is the primary psychoactive component with analgesics effects, while CBD is a non-psychoactive component with anti-inflammatory, analgesic, and antipsychotic properties.[4] 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 derivate mimicking THC) and nabiximols (i.e., THC and CBD).[5] 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.[6] 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.[3,5]

Both THC and CBD are metabolized by the drug metabolizing enzymes of the cytochrome P450 (CYP-450) system.[7] The CYP1A2, CYP2C9 and CPY3A4 enzymes are responsible for the metabolism of numerous prescribed medications as well as exogenous cannabinoids.[7,8] In vitro and ex vivo studies have shown that exogenous cannabinoids may act as substrates, inhibitors or inducers of various CYP-450 isoforms.[8] 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

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

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[10] are summarized below and presented in Appendix 2.

Study Design

The SR[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.

Country of Origin

The SR was from Canada and was published in 2016.[10]

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.

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.

Outcomes

The outcomes were pain, anxiety, sleep disturbance, and adverse drug reactions, including precautions and contraindications, drug-drug interactions, abuse potential, and dosing.[10]

Follow-up Period

The follow-up period of the included studies was not reported.

Data Analysis and Synthesis

The findings of drug-drug interactions were narratively described without providing any data.

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[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

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.

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.

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

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2. Temple LM. Medical marijuana and pain management. Dis Mon. 2016 Sep;62(9):346-52.
3. Consumer information-cannabis (marihuana, marijuana) [Internet]. Ottawa: Health Canada; 2017. [cited 2017 Apr 5]. Available from: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/marihuana/info/cons-eng.pdf
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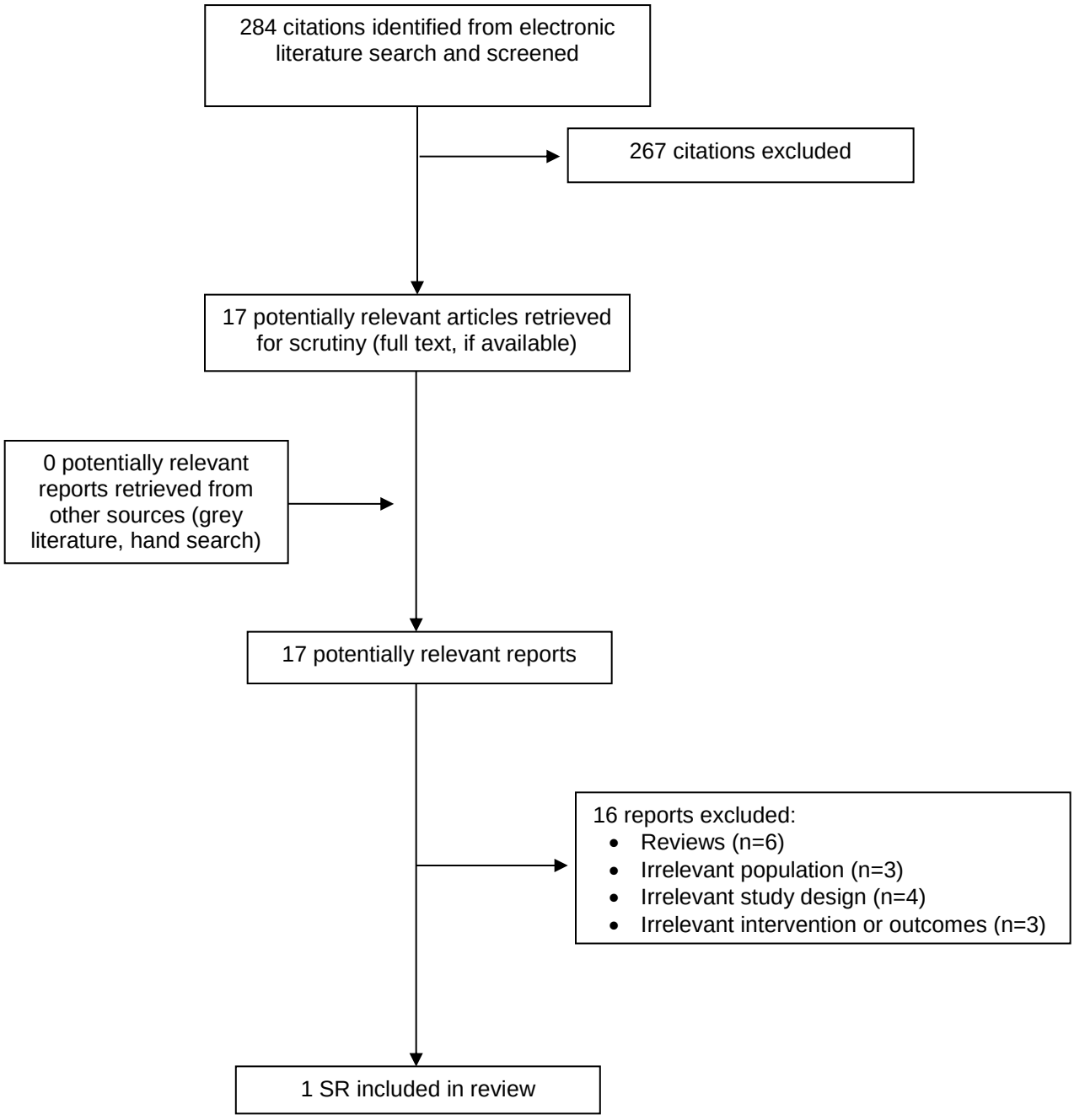
6. Statement from Health Canada concerning access to cannabis for medical purposes [Internet]. Ottawa: Health Canada; 2016 Aug 11. [cited 2017 Apr 5]. Available from: http://news.gc.ca/web/article-en.do?nid=1110389
7. Tai S, Fantegrossi WE. Pharmacological and toxicological effects of synthetic cannabinoids and their metabolites. Curr Top Behav Neurosci. 2016 Dec 24.
8. Stout SM, Cimino NM. Exogenous cannabinoids as substrates, inhibitors, and inducers of human drug metabolizing enzymes: a systematic review. Drug Metab Rev. 2014 Feb;46(1):86-95.
9. Methodology checklist 1: systematic reviews and meta-analyses [Internet]. Edinburgh, UK: Scottish Intercollegiate Guidelines Network; 2004. [cited 2017 Mar 29]. Available from: http://www.sign.ac.uk/pdf/sign50annexc.pdf
10. Tsang CC, Giudice MG. Nabilone for the management of pain. Pharmacotherapy. 2016 Mar;36(3):273-86.

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Studies

Table A1: Characteristics of Included Systematic Reviews

First Author, Publication Year, Country, Funding	Types and Numbers of Primary Studies Included	Population Characteristics	Interventions	Comparators	Clinical Outcomes, Length of Follow-up
Tsang and Giudice, 2016[10] Canada Funding: NR	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	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	Nabilone	Placebo or no treatment	• Pain • Anxiety and sleep disturbance • Adverse drug reactions including precautions and contraindications, drug interactions, abuse potential • Dosing Follow-up: NR

NR = not reported; RCT = randomized controlled trial; SR = systematic review

Appendix 3: Quality Assessment of Included Studies

Table A2: Quality Assessment of Systematic Reviews

SIGN Checklist: Internal Validity	Tsang and Giudice, 2016[10]
1. The research question is clearly defined and the inclusion/exclusion criteria must be listed in the paper	Yes
2. A comprehensive literature search is carried out	Yes
3. At least two people should have selected studies	Not reported
4. At least two people should have extracted data	Not reported
5. The status of publication was not used as an inclusion criteria	Yes
6. The excluded studies are listed	No
7. The relevant characteristics of the included studies are provided	Yes
8. The scientific quality of the included studies was assessed and reported	No
9. Was the scientific quality of the included studies used appropriately?	No
10. Appropriate methods are used to combine the individual study findings	Not applicable
11. The likelihood of publication bias was assessed appropriately	Not applicable
12. Conflicts of interest are declared	No
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.

Appendix 4: Main Study Findings and Author's Conclusions

Table A3: Summary of Findings of Included Systematic Reviews

<table>
<tr><th>Main Study Findings</th><th>Author's Conclusions</th></tr>
<tr><td colspan="2">Tsang and Giudice, 2016[10]</td></tr>
<tr><td>Drug-drug interactions (from two primary studies)
<table>
<tr><th>Medical Cannabis</th><th>Concomitant drugs</th><th>Clinical effects</th></tr>
<tr><td>Nabilone</td><td>Diazepam, alcohol, codeine</td><td>Additive central nervous system depressant effects</td></tr>
<tr><td>Nabilone</td><td>Opioids</td><td>Opioid-sparing effects</td></tr>
<tr><td>Nabilone</td><td>NSAIDs, TCAs, dexamethasone, ondansetron</td><td>Decrease the need for those drugs</td></tr>
</table></td><td>No conclusion regarding drug-drug interactions</td></tr>
</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

Stout SM, Cimino NM. Exogenous cannabinoids as substrates, inhibitors, and inducers of human drug metabolizing enzymes: a systematic review. Drug Metab Rev. 2014 Feb;46(1):86-95.

Primary Studies

No Comparator

Geffrey AL, Pollack SF, Bruno PL, Thiele EA. Drug-drug interaction between clobazam and cannabidiol in children with refractory epilepsy. Epilepsia [Internet]. 2015 Aug [cited 2017 Mar 23];56(8):1246-51. Available from: http://onlinelibrary.wiley.com/doi/10.1111/epi.13060/epdf

Case Reports

Richtig G, Bosse G, Arlt F, von Heymann C. Cannabis consumption before surgery may be associated with increased tolerance of anesthetic drugs: a case report. Int J Case Rep Images [Internet].2015 [cited 2017 Mar 23];6(7):436–439. http://www.ijcasereportsandimages.com/archive/2015/007-2015-ijcri/CR-10534-07-2015-richtig/ijcri-1053407201534-richtig-full-text.php

Karam K, Abbasi S, Khan FA. Anaesthetic consideration in a cannabis addict. J Coll Physicians Surg Pak. 2015 Apr;25 Suppl 1:S2-S3.

Hauser N, Sahai T, Richards R, Roberts T. High on cannabis and calcineurin inhibitors: a word of warning in an era of legalized marijuana. Case Rep Transplant [Internet]. 2016 [cited 2017 Mar 28];2016:4028492. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4993910

Jamil M, Zafar A, Adeel FS, Zawar I. Stroke from vasospasm due to marijuana use: can cannabis synergistically with other medications trigger cerebral vasospasm? Case Rep Neurol Med [Internet]. 2016 [cited 2017 Feb 21];2016:5313795. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5090067

Patient Population were Healthy Adults

Kollins SH, Schoenfelder EN, English JS, Holdaway A, Van Voorhees E, O'Brien BR, et al. An exploratory study of the combined effects of orally administered methylphenidate and delta-9-tetrahydrocannabinol (THC) on cardiovascular function, subjective effects, and performance in healthy adults. J Subst Abuse Treat [Internet]. 2015 Jan [cited 2017 Feb 21];48(1):96-103. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4250392

Ranganathan M, Carbuto M, Braley G, Elander J, Perry E, Pittman B, et al. Naltrexone does not attenuate the effects of intravenous Delta^9-tetrahydrocannabinol in healthy humans. Int J Neuropsychopharmacol. 2012 Oct;15(9):1251-64.

Manini AF, Yiannoulos G, Bergamaschi MM, Hernandez S, Olmedo R, Barnes AJ, et al. Safety and pharmacokinetics of oral cannabidiol when administered concomitantly with intravenous fentanyl in humans. J Addict Med [Internet]. 2015 May [cited 2017 Feb 21];9(3):204-10. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4449284

Hartman RL, Brown TL, Milavetz G, Spurgin A, Gorelick DA, Gaffney G, et al. Controlled cannabis vaporizer administration: blood and plasma cannabinoids with and without alcohol. Clin Chem [Internet]. 2015 Jun [cited 2017 Mar 29];61(6):850-69. Available from: http://clinchem.aaccjnls.org/content/clinchem/61/6/850.full.pdf

Narrative Reviews

Tai S, Fantegrossi WE. Pharmacological and toxicological effects of synthetic cannabinoids and their metabolites. Curr Top Behav Neurosci. 2016 Dec 24.

Russo EB. Current therapeutic cannabis controversies and clinical trial design issues. Front Pharmacol [Internet]. 2016 [cited 2017 Mar 28];7:309. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5022003

O'Connell BK, Gloss D, Devinsk O. Cannabinoids in treatment-resistant epilepsy: a review. Epilepsy Behav. 2017 Feb 7.

Lindsey WT, Stewart D, Childress D. Drug interactions between common illicit drugs and prescription therapies. Am J Drug Alcohol Abuse. 2012 Jul;38(4):334-43.

Gaston TE, Friedman D. Pharmacology of cannabinoids in the treatment of epilepsy. Epilepsy Behav. 2017 Jan 10.

Scavone JL, Sterling RC, Van Bockstaele EJ. Cannabinoid and opioid interactions: implications for opiate dependence and withdrawal. Neuroscience [Internet]. 2013 Sep 17 [cited 2017 Mar 29];248:637-54. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3742578

Kumar S, Rao PS, Earla R, Kumar A. Drug-drug interactions between anti-retroviral therapies and drugs of abuse in HIV systems. Expert Opin Drug Metab Toxicol [Internet]. 2015 Mar [cited 2017 Mar 29];11(3):343-55. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4428551