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SUMMARY WITH CRITICAL APPRAISAL**

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

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Abbreviations

CYP450	Cytochrome P450
THC	Tetrahydrocannabinol

Context and Policy Issues

According to Statistics Canada's National Cannabis Survey, approximately 2.7 million Canadians (9%) reported using cannabis for medical reasons in the first half of 2019.¹

For the purposes of this report, medical cannabis refers to use of the cannabis plant or its extracts or synthetic cannabinoids for medical purposes.

The list of medical conditions for which cannabis may be of benefit is extensive and includes chemotherapy-induced nausea and vomiting, cachexia, anorexia nervosa, multiple sclerosis, amyotrophic lateral sclerosis, spinal cord injury and disease, epilepsy, pain, and many others.²

The cannabis plant contains hundreds of pharmacological components, not all of which are well-characterized. Presence and quantity of these components varies considerably between plants and products, and even within a single plant. Tetrahydrocannabinol (THC) is the most well-studied and is the primary pharmacological component responsible for the psychoactive and physical effects of cannabis. Cannabidiol (also commonly referred to as CBD) is the second most prevalent pharmacologically active compound. It does not have psychotropic properties, but is also proposed to be of value for treatment of a wide variety of medical conditions.^{2,3} Producers of cannabis and cannabis extracts for medical purposes are able to supply products with specific desired quantities and ratios of THC and cannabidiol.² Two medical cannabis products are currently marketed for use in Canada. Nabiximols (Sativex) is a prescription product containing THC and cannabidiol. Nabilone (Cesamet) is a prescription synthetic cannabinoid product available in Canada. Synthetic cannabinoids mimic the effects of the active components of cannabis.⁴

Cytochrome P450 (CYP450) enzymes play a crucial role in the metabolism of many medications and are the main drivers of pharmacokinetic drug interactions. THC and cannabidiol are known substrates and modulators of the CYP450 enzyme system. THC and cannabidiol have shown to inhibit several CYP450 enzymes in vitro, whereas smoke from cannabis may induce one specific CYP450 enzyme. Along with a lack of robust clinical studies, inconsistency in chemical make-up and method of ingestion of various cannabis products makes it particularly difficult to clinically assess for and predict interactions between cannabis and other medications. In addition to the potential pharmacokinetic interactions due to changes in drug metabolism, the risk of pharmacodynamic interactions (e.g., adverse effects secondary to the use of cannabis with other psychoactive drugs) is also important to consider.^{3,5}

The aim of this report is to review the evidence surrounding safety of medical cannabis in combination with other medications, and relevant evidence-based guidelines.

This is an update of a previous report published in April 2017, which found a single systematic review, and no evidence-based guidelines.⁶

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 drug interactions between medical cannabis and other medications?

Key Findings

Evidence of limited quality from two studies of oral cannabidiol in combination with other antiepileptic drugs indicated that cannabidiol may increase serum levels of clobazam. One of these two studies also found that oral cannabidiol may increase serum levels of eslicarbazepine, topiramate, zonisamide, and rufinamide. This evidence was limited by a high risk of bias and may not be generalizable to the Canadian context. Additionally, only antiepileptic drugs were studied.

No evidence-based guidelines surrounding drug interactions with medical cannabis were found.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including PubMed, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were drug interactions and use of medical cannabis. 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, 2017 and August 26, 2019.

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	Medical cannabis with the use of other medications (including illicit substances and alcohol)
Comparator	Q1: Other medications alone, including illicit substances and alcohol Q2: No Comparator
Outcomes	Q1: Drug-drug interactions, safety, harms Q2: Guidelines (e.g., recommendations on the use of medical cannabis interacting with other medications including dosage)

Study Designs

Q1: Health Technology Assessments, Systematic Reviews, Meta-Analyses, Randomized controlled trials, Non-randomized studies
Q2: Evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2017. Case reports and guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The included studies were critically appraised using ROBINS-I⁷ by one reviewer. Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 299 citations were identified in the electronic database search. Following screening of titles and abstracts, 283 citations were excluded and 16 potentially relevant reports from the electronic search were retrieved for full-text review. Nine potentially relevant publications were retrieved from the grey literature search for full text review. Of these 25 potentially relevant articles, 23 were excluded, and two non-randomized (for the comparisons of interest) studies met inclusion criteria. No evidence-based guidelines were found. Appendix 1 presents the PRISMA⁸ flowchart of the study selection.

Summary of Study Characteristics

A summary of characteristics of included publications is provided in Appendix 2.

Study Design

Wheless et al.⁹ conducted a randomized phase I/II multiple-dose study aiming to characterize the pharmacokinetics and tolerability of a cannabidiol solution. Sixty-one pediatric patients were randomly assigned to receive one of three doses of the oral cannabidiol solution for treatment-resistant epilepsy. Within this study, the interaction between clobazam and oral cannabidiol solution was assessed for a subgroup of patients (n = 32) who were receiving clobazam at study entry. Clobazam and norclobazam concentrations were compared at baseline and day 10.

Gaston et al.¹⁰ conducted an open-label prospective study of 42 pediatric and 39 adult patients receiving cannabidiol and concomitant antiepileptics. A relevant comparison of antiepileptic serum drug levels at baseline and after starting cannabidiol was performed. Participants had serum antiepileptic levels measured at baseline prior to enrollment, and at several time periods after starting cannabidiol. Investigators were permitted to adjust doses of antiepileptic drugs throughout the study period.

Country of Origin

Both included studies were conducted in the United States.

Patient Population

Wheless et al.⁹ included 61 children between 1 and 17 years old with treatment-resistant epilepsy. Mean age was 7.6 years; comprised of five infants (age 1 year), 28 children (age 2-11 years) and 18 adolescents (age 12-16 years). Among the 61 patients, 67% were female, mean weight was 27 kg, and baseline mean frequency of seizures was 16 per day. Patients receiving medications known to induce or inhibit CYP450 enzymes or that were receiving a known CYP450 substrate with a narrow therapeutic window were excluded. The subgroup of 32 participants receiving clobazam at study entry are of relevance to this report. Characteristics of this subgroup were not described separately.

Gaston et al.¹⁰ included 42 pediatric (at least 1 year of age) and 39 adult (age 19 years and older) patients with treatment-resistant epilepsy. In order to be eligible for inclusion, participants were on a stable dose of other antiepileptic drugs for at least one month prior to enrollment. The mean age in the pediatric arm was 10.4 years and in the adult arm was 29.1 years. The pediatric arm was 52% male and adult 51% female. In the pediatric arm participants were taking a mean of 3.0 antiepileptic drugs at enrollment, and 3.2 in the adult arm.

Interventions and Comparators

In Wheless et al.⁹ participants were randomized to receive one of three doses synthetic cannabidiol as an oral solution: 10 mg/kg/day (n = 20), 20 mg/kg/day (n = 20), or 40 mg/kg/day (n = 21) of cannabidiol. A subgroup of 32 patients were taking clobazam at baseline and throughout the study; dose of clobazam was not provided. Comparison of serum clobazam and norclobazam levels was made between day 0 (baseline) and day 10 of cannabidiol treatment. Norclobazam is the active metabolite of clobazam.

In Gaston et al.,¹⁰ participants were initiated on a prescription cannabidiol solution (Epidiolex) 5 mg/kg/day divided into two doses per day. The dose could be titrated by 5mg/kg increments at each visit (every two weeks) up to 50 mg/kg/day. Participants continued other antiepileptic drugs, and antiepileptic doses were adjusted at the discretion of the treating physician. Serum drug levels were compared at baseline versus after starting cannabidiol for patients taking clobazam, eslicarbazepine, topiramate, zonisamide, and rufinamide.

The oral cannabidiol solutions used in both of the above studies are not marketed in Canada.

Outcomes

Wheless et al.⁹ reported serum clobazam and norclobazam levels at day 0 and day 10.

Gaston et al.¹⁰ compared serum drug levels of clobazam, N-desmethyloclobazam (i.e., norclobazam, the active metabolite of clobazam), eslicarbazepine, topiramate, zonisamide and rufinamide before initiation of cannabidiol and at the first two clinic visits, two and four weeks after starting cannabidiol. The investigators also performed a sub-analysis of aspartate transaminase (AST) and alanine transaminase (ALT; liver enzymes) in patients receiving valproic acid; however, no comparison relevant to this report was made (i.e., there was no comparison of AST and ALT levels with valproic acid plus cannabidiol versus with valproic acid alone).

Summary of Critical Appraisal

Risk of bias for Wheless et al.⁹ was assessed specifically for outcomes related to the interaction between clobazam and cannabidiol, as this was the outcome of interest for this report. Assessment of the interaction of clobazam and cannabidiol was not a primary aim of the study, and the assessment of risk of bias for this outcome is not relevant to other study outcomes. Risk of bias was deemed to be high for the comparison clobazam plus cannabidiol (at day 10) versus clobazam alone (baseline). No potential confounders (e.g., adherence, timing of levels or doses of the antiepileptics, other medication changes) were considered or accounted for in this comparison. The comparison was made between baseline and day 10 in the same participants, which also introduces potential for time-varying confounding; however, it is unclear whether a span of 10 days between measurements would have a meaningful impact on the results. The reported “up to 2.8-fold” difference in clobazam concentration indicates possible selective reporting of the most clinically significant result; outcome measurements and analyses with respect to clobazam concentrations may have been performed that were not reported. Although the study was open-label, the objective outcome measures (clobazam levels, norclobazam levels) would not have been influenced by knowledge of intervention received.

Risk of bias was also deemed to be high for the relevant outcomes assessed in Gaston et al.¹⁰ Measurement of clobazam and valproic acid concentrations was performed at baseline and first and/or second follow-up visits to assess for the presence of an interaction between antiepileptic drug and cannabidiol. No potential confounders (e.g. adherence, timing of levels or doses of the antiepileptics, other medication changes) were considered or accounted for in this comparison. Additionally, antiepileptic dose was adjusted at the discretion of the treating physician. The comparison between baseline and follow-up in the same participants also introduces the potential for time-varying confounding, though it is unclear whether this potential bias would meaningfully impact the findings. Although the study was open-label, the objective outcome measures would not have been influenced by knowledge of intervention received. However, frequency of monitoring and providers’ likelihood of intervening on an increased level may have changed due to knowledge of the study intervention.

A summary of the strengths and limitations of included publications are provided in Appendix 3.

Summary of Findings

Primary clinical studies

Wheless et al.⁹ found an increase in clobazam concentrations between baseline and day 10, as well as differences in clobazam concentrations among patients receiving different doses of cannabidiol. Mean clobazam concentrations were 1.7-fold and norclobazam 1.3-fold higher with cannabidiol 40mg/kg/day versus 10mg/kg/day, and were 2.2-fold and 1.9-fold higher for 40mg/kg/day versus 20mg/kg/day. At day 10 of cannabidiol (any dose) as compared to baseline for patients on clobazam, mean clobazam and norclobazam concentrations increased up to 2.8-fold. No other analyses relevant to these results were provided. The authors suggest that close monitoring of concentration and clinical effect may be warranted in patients receiving clobazam and cannabidiol concomitantly.

Gaston et al.¹⁰ found a statistically significant increase in mean serum clobazam, N-desmethyloclobazam (a metabolite of clobazam), and eslicarbazepine levels at two and four

weeks as compared to baseline. Serum drug levels increased to above the normal therapeutic range for clobazam and N-desmethyloclobazam. The increase in serum drug levels tended to be higher in the subgroup of patients that had their antiepileptic dose reduced. It is possible that patients requiring dose reduction may have experienced symptoms of toxicity, which may reflect higher serum drug levels in patients in this subgroup; however, this finding was not explored or explained in the study. Levels also increased for topiramate, zonisamide, and rufinamide, although these increases were not statistically significant. The authors concluded that monitoring of serum levels of antiepileptics on initiation of cannabidiol is important, and that controlled pharmacokinetic studies are warranted.

Appendix 4 presents a table of the main study findings and authors' conclusions.

Guidelines

No evidence-based guidelines addressing the clinical question were identified.

Limitations

Despite its use for a variety of medical conditions and known effects on enzymes implicated in the metabolism of the other medications, evidence surrounding drug interactions with medical cannabis is sparse. Studies published since the previous CADTH report are limited to antiepileptic drugs, have a high risk of bias for the outcomes of relevance to this report, and assessed only non-clinical outcomes with short duration of follow-up (up to four weeks). Additionally, the prescription cannabidiol solutions used in these studies are not currently marketed in Canada, thus limiting the generalizability of these findings to the Canadian context. Given that medical cannabis can be used for a number of different conditions for which drug interactions could be of significant consequence, this represents a significant research gap.

Conclusions and Implications for Decision or Policy Making

Two studies measured clobazam drug concentrations before and after initiation of cannabidiol for treatment-resistant epilepsy.^{9,10} Levels of clobazam and its active metabolite increased after initiation of cannabidiol in both studies. In one of these studies, concentrations of eslicarbazepine, topiramate, zonisamide, and rufinamide also increased; only the changes in eslicarbazepine and clobazam levels were statistically significant.¹⁰ Statistical significance was not evaluated in the other study, though the reported increase could be expected to be clinically meaningful.⁹

Application of this evidence is limited by a high risk of bias associated with these outcomes and the unavailability of the studied cannabidiol solutions in Canada. Furthermore, studies evaluating the use of medical cannabis and concomitant medications for conditions other than epilepsy were not identified for this review.

This report updates and adds to the findings of a 2017 CADTH report,⁶ which included a single systematic review addressing the research question. The report found evidence from one systematic review of two relevant studies that reported on a possible additive depressant effect when nabilone is taken concomitantly with diazepam and codeine and a decrease in need for other medications including analgesics and antiemetics in patients with pain conditions.⁶

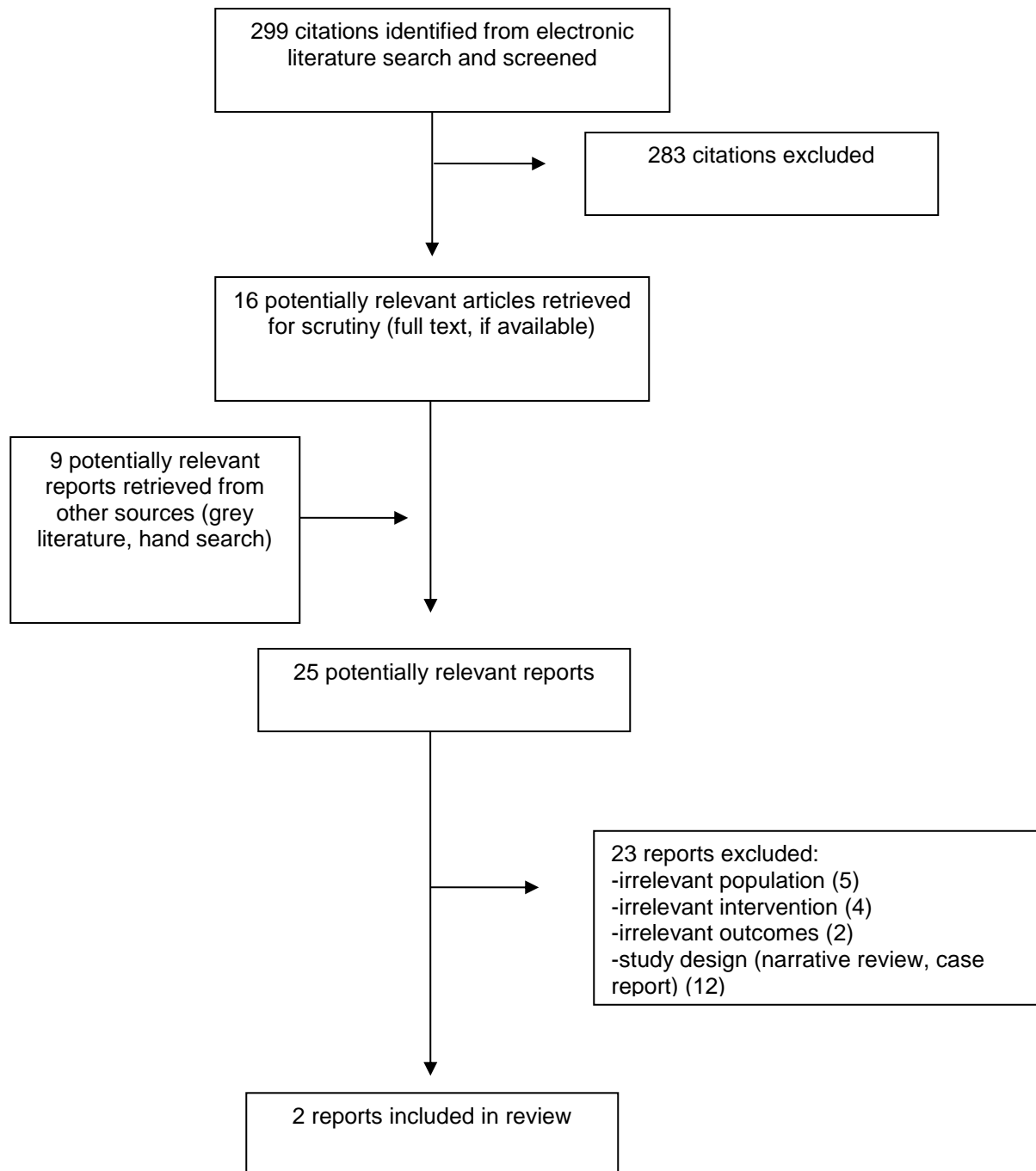
Based on the ability of both THC and cannabidiol to modulate the metabolic pathway for many drugs, and their potential to have additive pharmacologic effects with drugs commonly used for conditions for which they are used therapeutically, the potential for drug interactions with cannabis is an important concern. The lack of evidence-based guidelines is not surprising, given the limited quantity and quality of available evidence on the subject.

Studies of cannabis products available in Canada, randomizing participants who are receiving concomitant medications to medical cannabis versus placebo or no treatment and assessing clinical and pharmacokinetic outcomes, would reduce uncertainty.

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Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Wheless, 2019⁹ USA	Phase 1/2 open-label randomized controlled trial aiming to assess pharmacokinetics and safety of 3 doses of a synthetic cannabidiol solution. (n=61) Within this study there was a relevant before and after comparison of clobazam concentrations in participants receiving clobazam at baseline (n=32).	-Children between 1 and 17 years old with treatment-resistant epilepsy -32 participants were receiving concomitant clobazam (subgroup of interest for this report) -Mean age 7.6 (SD 5.2) -67% Female -Mean weight 26.9kg (SD 17.4) -Mean 16.1 seizures per day (SD 25.0) at baseline	Intervention: -Cannabidiol oral solution 10mg/kg/day -Cannabidiol oral solution 20mg/kg/day -Cannabidiol oral solution 40mg/kg/day Comparison: -Baseline (no cannabidiol) Participants of relevance to this report were receiving concomitant clobazam at baseline and for the duration of the study Cannabidiol total daily dose was divided into 2 doses per day	-Clobazam and norclobazam concentrations at 0 and 10 days
Gaston, 2017¹⁰ USA	Open-label, prospective study of 42 pediatric and 39 adult patients receiving cannabidiol and concomitant antiepileptics. Relevant comparison of antiepileptic serum drug levels at baseline and after starting cannabidiol was performed.	Age > 1 year, stable dose of antiepileptic drugs for at least 1 month prior to enrollment. Pediatric arm: -Mean age 10.4 (SD 5.3) -52% male -Mean 3.0 (SD 1) antiepileptic drugs at enrollment Adult arm: -Mean age 29.1 (SD 11.3) -51% female -Mean 3.2 (SD 0.9) antiepileptic drugs at enrollment	Intervention: Cannabidiol (Epidiolex) 5-50mg/kg/day (divided into 2 doses per day) plus baseline antiepileptic drugs Comparison: antiepileptic drugs at baseline	-Serum levels of antiepileptic drugs

SD = standard deviation;

Appendix 3: Critical Appraisal of Included Publications

Table 3: Strengths and Limitations of Clinical Studies using ROBINS-I⁷

Strengths	Limitations
Wheless, 2019 ⁹	
<ul style="list-style-type: none"> -Objective outcome measure -Randomization to different doses of the intervention allowed for assessment of possible dose-response relationship 	<ul style="list-style-type: none"> -Critical risk of bias due to confounding (including time-varying confounding) for the relevant before-and-after comparison of clobazam/norclobazam levels; confounding was not considered or addressed -Possibility for multiple outcome measurements/analyses within the outcome domain and selective reporting -Analysis of the interaction between clobazam and cannabidiol was not a primary aim of the study
Gaston, 2017 ¹⁰	
<ul style="list-style-type: none"> -Objective outcome measure -A comparison of drug levels was made prior to dose adjustment of concomitant antiepileptics -Pragmatic approach increases external validity 	<ul style="list-style-type: none"> -Critical risk of bias due to confounding (including time-varying confounding) for relevant outcomes; confounding variables other than dose of antiepileptic were not considered or addressed

Appendix 4: Main Study Findings and Authors' Conclusions

Table 4: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Wheless, 2019 ⁹	
<p>CBD (all doses) day 10 vs day 0 (n = 32): Mean clobazam and norclobazam concentrations increased up to 2.8-fold</p> <p>CBD 40mg/kg/day vs 10mg/kg/day: Mean clobazam concentrations 1.7-fold and norclobazam 1.3-fold higher</p> <p>CBD 40mg/kg/day vs 20mg/kg/day: Mean clobazam concentrations 2.2-fold and norclobazam 1.9-fold higher</p>	<p>"close serum concentration monitoring for both medications along with clinical monitoring may be needed in pediatric patients receiving clobazam concomitantly with cannabidiol." (p. 602)</p>
Gaston, 2017 ¹⁰	
<p>Comparison of antiepileptic drug levels at baseline and at two and four weeks after initiation of CBD (Table 3 p.1590):</p> <p>Clobazam (n = 27, p = 0.03 for change from baseline) Baseline 264.7ng/mL First follow-up: 331.17ng/mL (antiepileptic dose unchanged) and 430.3ng/mL (antiepileptic dose decreased) Second follow-up: 310.97ng/mL (antiepileptic dose unchanged) and 285.0ng/mL (antiepileptic dose decreased)</p> <p>N-desmethyclobazam (n = 26, p < 0.001 for change from baseline) Baseline 2,207.5ng/mL First follow-up: 3,727.77ng/mL (antiepileptic dose unchanged) and 6,226.87ng/mL (antiepileptic dose decreased) Second follow-up: 3,696.87ng/mL (antiepileptic dose unchanged) and 4,843.87ng/mL (antiepileptic dose decreased)</p> <p>Eslicarbazepine (n = 4, p = 0.008 for change from baseline) Baseline: 14.4 mcg/mL First follow-up: 16.8mcg/mL Second follow-up: 17.8 mcg/mL</p> <p>Topiramate (n = 20, p > 0.05) Baseline: 10.3mcg/mL First follow-up: 10.8mcg/mL Second follow-up: 11.3mcg/mL</p> <p>Zonisamide (n = 14, p > 0.05) Baseline: 17.2mcg/mL First follow-up: 19.3mcg/mL Second follow-up: 17.2mcg/mL (antiepileptic dose unchanged) and 42mcg/mL (antiepileptic dose decreased in 1 adult)</p> <p>Rufinamide (n = 14, p > 0.05) Baseline: 24.8mcg/mL First follow-up: 25.6mcg/mL Second follow-up: 27.0mcg/mL</p>	<p>"This study introduces potential pharmacokinetic interactions between CBD and other commonly used AEDs in the treatment of epilepsy. Because CBD continues to be studied as a potential anticonvulsant, clinicians and researchers alike should be aware of significant changes in serum levels of clobazam/desmethylclobazam, eslicarbazepine, rufinamide, topiramate, and zonisamide. In addition, although this is part of routine drug monitoring, liver function should be monitored closely in patients taking concomitant CBD and valproate, as this combination may result in an increase in both AST and ALT levels. Going forward, formal pharmacokinetic studies under controlled conditions will be needed to further confirm these interactions."(p.1591)</p>

AEDs = antiepileptic drugs; CBD= cannabidiol.