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REVIEW ARTICLE

Clinical guidance for cannabidiol-associated hepatotoxicity: A narrative review

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Abstract

There is increasing evidence that cannabidiol (CBD) use is associated with clinically significant liver enzyme (LE) elevations and drug-induced liver injury (DILI). The proportion of LE elevations and DILI events reported in the literature meet the Council for International Organizations of Medical Sciences' (CIOMS) classification of a common adverse drug reaction. However, these potential adverse events are unknown to many clinicians and may be overlooked. The increasing use of CBD for both medical and non-medical use necessitates clear direction in the diagnosis and management of CBD-associated hepatotoxicity. To our knowledge, no such clinical guidance currently exists. For people presenting with elevated LEs, CBD use should be screened for and be considered in the differential diagnosis. This narrative review will provide clinicians with guidance in the prevention, detection, and management of CBD-related hepatotoxicity.

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Introduction

Cannabidiol (CBD) use and access is increasing worldwide.[1] Despite the common perception that CBD is not associated with any severe adverse effects, there is emerging evidence of hepatotoxicity associated with CBD use.[2–4] As a result, there is a need for a better clinical framework for detecting, preventing, and managing CBD-associated hepatotoxicity. These considerations are pertinent for healthcare providers (HCPs) to be aware of, especially in areas of the world where CBD is widely available.

CBD is one of the main phytocannabinoids found in cannabis. This 21-carbon terpenophenolic compound has complex pharmacodynamics with new molecular targets emerging.[5] CBD has low affinity for both cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2)[6] with non-competitive negative allosteric modulation of both.[7,8] CBD acts as an inverse agonist of CB1 and CB2.[9] In the presence of CB1 and CB2 agonists, CBD antagonizes their effects.[7] These effects are a stark contrast from tetrahydrocannabinol's (THC) strong CB1 agonism.[9] CBD also interacts with several non-cannabinoid receptors including positive allosteric modification of the serotonin 1A receptor, activation (leading to eventual desensitization) of the vanilloid receptor 1, inhibition of fatty acid amide hydrolase, and activation of peroxisome proliferator-activated receptor γ (PPARγ) to name a few.[7,9–13] Through these direct and indirect interactions, CBD can modulate a large variety of physiological systems. Clinically, this has correlated to interest in CBD as an analgesic, anti-inflammatory, anxiolytic, antipsychotic and anticonvulsant.[14,15]

The global rise in legal cannabis and cannabinoid product access for both medical and non-medical purposes has led to their increased promotion and usage. North America, particularly, has the highest cannabis use rates.[16–19] Of the cannabinoids available, CBD has gained notable popularity. One American commercial survey reported that the majority of Americans have heard of CBD, while 14–18% of respondents had tried or were currently using CBD products.[20,21] Other surveys report over 60% of respondents have tried a CBD product.[22] Additional data show CBD usage was 26.1% among Americans and 16.2% among Canadians.[21,23,24] In one cross-sectional study on people who use CBD, 62% reported they utilized it to manage a medical condion.[25] Common reasons for CBD use include managing pain, anxiety, and depression.[21]

This narrative review aims to provide a practical overview and clinical recommendations for mitigating and managing CBD-associated hepatotoxicity. The American College of

Gastroenterology (ACG) Clinical Guideline for the Diagnosis and Management of Idiosyncratic Drug-Induced Liver Injury and the American Association for the Study of Liver Diseases (AASLD) practice guidance on drug, herbal, and dietary supplement-induced liver injury will be used as a framework in the clinical diagnosis and management of CBD-associated hepatotoxicity.[26,27] Key recommendations are presented in Table 1. Dosing categories and monitoring recommendations are presented in Table 2.

Drug-induced liver injury

Liver enzyme (LE) (e.g., alanine transaminase [ALT], alkaline phosphatase [ALP], aspartate aminotransferase [AST], gamma-glutamyl transpeptidase [GGT]) elevation is a commonly seen phenomenon with drug administration and is often harmless, transient, and may resolve despite continuation of the offending drug.[29,30] However, a significant elevation in LEs or abnormalities in liver function tests (LFTs), (bilirubin and/or international normalized ratio [INR]), after the administration of a new drug can be indicative of drug-induced liver injury (DILI).[31,32] The diagnosis of DILI can be challenging due to the wide range of presentations and lack of reliable clinical or diagnostic testing.[33,34] Histological manifestations on liver biopsy also fail to show distinct findings for DILI and can appear similar to other etiologies of acute or chronic liver injury.[33,35] DILI tends to be a diagnosis of exclusion.[33,34,36] A full medication, recreational substance, herbal, and dietary supplement review is crucial in making the diagnosis, with a focus on drug onset, dose, duration of use, and previous exposures.[31,34] To improve future diagnostic process, projects are currently underway to determine potential biomarkers associated with the various mechanisms of DILI, including genomics, transcriptomics, proteomics, and metabolomics.[37]

DILI is biochemically divided into three categories (hepatocellular, cholestatic, or mixed) based on the *R* value, a normalized ratio of serum ALT and ALP[28,38] (see Table 3). Categorizing DILI using the *R* value can give insight into which medication is the culprit, clarify the mechanism of liver injury, guide investigations to rule out alternative diagnoses, and give prognostic value.[31,32,35] The *R* value is usually calculated at time of initial presentation as LEs can change precipitously and markedly over time.[32,36]

Overview of CBD-associated liver injury

Risk and probability. A recent meta-analysis showed that when compared with placebo controls, CBD was associated with a higher risk of LE elevation (odds ratio [OR] = 5.85; 95% confidence interval [CI] = 3.84–8.92, $P < 0.001$) and DILI (OR = 4.82; 95% CI = 2.46–9.45, $P < 0.001$).[2] This was seen in both medical and healthy populations. High-dose CBD and concomitant antiepileptic drug (AED) use were identified as risk factors (See the Risk factors of CBD-related hepatotoxicity section for more information).[2,40,41] No cases of severe DILI or liver failure were reported. Although most cases of elevated LEs resolved, it is important to note that participants with elevated LEs often had CBD discontinued or the dose reduced.[2] It is unknown if these cases would have progressed to severe DILI or acute liver failure if CBD were continued at the same dose.[2] The proportion of events (DILI = 2.96%; 95% CI 1.36–6.31) suggests that LE

Table 1 Key recommendations for cannabidiol (CBD)-associated hepatotoxicity

Key recommendations

- Do not initiate CBD if baseline LEs are > 3 × ULN without expert consultation.
- People with mildly elevated baseline aminotransferases (< 3 × ULN) or those taking concomitant medications that may be hepatotoxic (especially valproic acid) are at increased risk of CBD-associated hepatotoxicity.
- When initiating oral cannabis reaching or exceeding 300 mg of CBD daily, in people at increased risk of CBD-associated hepatotoxicity, monitoring with blood work (serum aminotransferases, ALP, INR, and total bilirubin levels) at baseline and every 2 weeks for the first 6 weeks, then monthly for the first 6 months is recommended.
- In people without these risk factors, initiating cannabis containing ≥ 300 mg of CBD monitoring with blood work (serum aminotransferases, ALP, INR, and total bilirubin levels) at baseline, 1, 3, and 6 months is recommended.
- If people have already been on ≥ 300 mg/day of oral CBD for ≥ 3 months, without baseline risk factors, they are likely at a low risk for CBD-associated hepatotoxicity. Clinical judgment should be used to determine if blood work is required.
- If aminotransferases are elevated > 3 × ULN **OR** ALP > ULN with bilirubin < 2 × ULN, repeat testing of LEs within 48–72 h is recommended.
- If LE elevations are sustained, but aminotransferases are < 5 × ULN, ALP < 2 × ULN and bilirubin < 2 × ULN, management approaches include reducing CBD dosage by 50% or reducing dose of other hepatotoxic medications the person may be taking and re-evaluating LEs in 7 days to ensure LEs are trending down.
  - This decision will be person-dependent, including an analysis of which medication (CBD *vs* other hepatotoxic medication) is most required therapeutically.
- CBD should be stopped in people who meet criteria for DILI:
  - ALT **OR** AST > 5 × ULN without symptoms on two separate occasions at least 24 hours apart
  - ALP > 2 × ULN, **OR** bilirubin > 2 × ULN with any rise of ALT and AST
  - ALT **OR** AST < 5 × ULN with symptoms associated with liver injury
  - INR > 1.5 with any elevation of serum AST, ALT, or ALP
- After discontinuing CBD in those with a DILI, it is recommended to monitor serum aminotransferases, ALP, INR, and total bilirubin levels weekly to assess DILI resolution.
  - If there is < 50% decline in peak ALT values at 30-days, consider alternative diagnoses and referral for consideration of liver biopsy[26,28]

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; CBD, cannabidiol; INR, international normalized ratio; ULN, upper limit of normal.

Table 2 Cannabidiol dosing categories and monitoring recommendations

Category[†]	Adult dosing (day)	Recommended monitoring in people at risk[‡]	Recommended monitoring for all other people
Low	< 300 mg	Not routinely required	Not routinely required
Moderate	≥ 300 to 999 mg	Baseline, and every 2 weeks for the first 6 weeks, then monthly for the first 6 months	Baseline, 1, 3, and 6 months
High	≥ 1000 to 1499 mg		
Very high	≥ 1500 mg		

[†]For details on dose categorization and study populations, see Lo *et al.*[2]; majority of evidence from epilepsy populations may not translate to other populations.
[‡]People at increased risk of CBD-associated hepatotoxicity include those with mildly elevated baseline aminotransferases (< 3 × ULN) or those taking concomitant medications that may be hepatotoxic (especially valproic acid). Risk stratification should still be judged on an individual basis. More frequent monitoring may be required in some cases based on the patient and clinical judgment.

Table 3 Biochemical categorization of drug-induced liver injury

Pattern of liver injury	Characterization	*R* value calculation
Hepatocellular ($R \geq 5$)	Characterized by a predominant rise in the level of aminotransferases. Usually results from hepatocellular damage via inflammation, apoptosis and/or necrosis.	$\frac{(ALT/ULN_{ALT})}{(ALP/ULN_{ALP})} \geq 5$
Cholestatic ($R \leq 2$)	Characterized by a predominant rise of the serum ALP levels. Usually results from bile stasis or primary injury to the bile ductular cells.	$\frac{(ALT/ULN_{ALT})}{(ALP/ULN_{ALP})} \leq 2$
Mixed ($2 < R < 5$)	Features of both hepatocellular and cholestatic injury may be present	$\frac{(ALT/ULN_{ALT})}{(ALP/ULN_{ALP})} > 2 \text{ to } < 5$

Abbreviations: ALT, alanine transaminase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; ULN, upper limit of normal.
Source: Adapted from other studies.[26,32,34,39]

elevation and DILI meet the Council for International Organizations of Medical Sciences' (CIOMS) classification of a common adverse drug reaction.[42]

In addition to LE elevation, bilirubin levels were elevated in some participants with CBD-associated DILI. Although bilirubin levels remained below 2 × ULN and resolved, they were elevated × 2–3 the baseline value in some cases. In all cases, CBD was discontinued or other medications (predominantly AEDs) were modified.[41,43]

Pathophysiology of CBD-related hepatotoxicity.

There are two main divisions in DILI pathophysiology: intrinsic and idiosyncratic hepatotoxicity. Intrinsic DILI is predictable, dose-dependent, and occurs within hours to days of exposure to the drug at a toxic threshold dose. Idiosyncratic DILI is less predictable, with a longer latency period and is thought to be influenced by individual and environmental factors.[31,32,34] Current evidence supports that idiosyncratic DILI is predominantly an immunologic phenomenon based on individual genetic susceptibility.[37] Specifically, there is increasing awareness of the association between the presence of specific human leukocyte antigen (HLA) alleles and an individual's risk of DILI to a particular agent.[37] Mitochondrial function may also be implicated. However, those with idiosyncratic DILI can lack features of drug hypersensitivity (fever, rash, arthralgias, and eosinophilia), as was seen in a review of isoniazid-induced DILI.[44] This, along with a propensity for idiosyncratic DILI in those of older age, shows that the clinical–pathological picture is beyond that of a pure immunologic phenomenon, and may include other hepatotoxic mechanisms, such as mitochondrial toxicity leading to oxidative hepatic injury.[44]

The natural history of CBD-associated DILI has features of both intrinsic and idiosyncratic hepatotoxicity. There are higher rates of hepatocellular-DILI in those receiving high doses of CBD, but even at high doses, there is inconsistency in who is affected (seen in both healthy and medical populations), and there is variability in time to DILI onset from CBD initiation, often occurring several weeks from the start of CBD administration.[2,45] Some, but not all, cases of CBD-associated DILI showed immune-related features with eosinophilia, rash, and/or abdominal pain and vomiting, a finding more frequently found in trials of healthy participants, but was also seen in several participants in the pediatric epilepsy trials.[29,46–49]

The underlying pathophysiology of CBD-associated hepatotoxicity is not fully understood. There are a number of possible theories based on molecular, biochemical, genetic, and animal studies. CBD regulates at least 50 genes, many of which are associated with lipid and drug metabolism.[50] CBD is also capable of modulating many cytochrome P450 (CYP) enzymes responsible for the metabolism of many pharmaceutical and herbal/dietary substances.[50] Current pharmacological evidence remains sparse and variable, with some studies showing liver-related benefits while others show detriments, likely influenced by differences in CBD dosing regimens, products utilized, and populations studied and their underlying comorbidities and concomitant medications.[10,51–53] This gives important insight into the need for further studies to delineate the mechanisms and explain the paradoxical findings seen in these studies.

Risk factors of CBD-related hepatotoxicity

Route of administration. All cases of DILI in the current literature were in individuals using oral CBD oil.[2] There is an absence of CBD-associated hepatotoxicity research using other routes of administration. Ingested CBD is metabolized directly by the liver while inhaled CBD is absorbed through the respiratory tract, thus bypassing first-pass hepatic metabolism.[54] As such, inhalation delivery has the potential to reduce concerns of hepatotoxicity that are associated with ingested CBD.[54] More research is needed to assess hepatotoxicity risk with inhalation and other routes of administration.

CBD dose. High-dose CBD (Table 2) use is a significant risk factor for LE elevations and DILI.[2,4,55] A recent meta-analysis showed that 77.36% of LE elevations and 89.47% of DILI cases occurred in individuals receiving oral CBD doses of $>$ 1000 mg/day.[2]

While dose does appear to be a significant risk factor, the risk of elevated LEs and DILI does not appear to be entirely dose dependent. There were reports of outlier cases of DILI in healthy adults taking a moderate dose of CBD ($>$ 300 to 999 mg).[56] Conversely, some studies reported no LE elevations in individuals receiving very high doses of CBD ($>$ 1500 mg).[48,57] This is further evidence that CBD is partially associated with idiosyncratic DILI, characterized as being unpredictable, loosely dose dependent but without evidence of a universally toxic threshold dose.[45]

Low doses of CBD ($<$ 300 mg) in adults were not associated with hepatotoxicity.[2,58,59] This is important to note as the vast majority of people use CBD at low doses. Provided that individuals are not taking concomitant medications that either inhibit the metabolism of CBD (see section on Concomitant medications) or have additional risk of hepatotoxicity, they are likely at low risk for LE elevations or DILI at these doses of CBD.

Concomitant medications. CBD has been associated with elevated LEs and DILI independent of other medications, but there appears to be increased risk with the concomitant use of certain medications, especially AEDs.[55,60] The majority of the reported cases in the literature of CBD-associated DILI or elevated LEs were in participants taking concomitant valproic acid (VPA) and to a lesser extent clobazam (CLB).[2,60] Individuals taking CBD who were on concomitant VPA were found to have significantly greater odds of LE elevations (OR = 6.92; 95% CI = 4.74–10.09, $P < 0.001$) and DILI (OR = 5.05; 95% CI = 2.20–11.60, $P < 0.001$) compared with those not taking VPA.[2] While most studies show no change in VPA and CBD pharmacokinetics with co-ingestion, there appears to be other, potentially pharmacodynamic, hepatotoxic effects when these medications are combined.[47,55,57,61,62]

Pharmacokinetic analysis of CLB reveals a clinically significant drug–drug interaction when CLB is co-administered with a moderate or strong CYP2C19 inhibitor such as CBD.[62,63] This results in an increased plasma concentration of norclobazam (nCLB), the active metabolite of CLB and is commonly associated with an increased risk of adverse effects.[64–66] It is hypothesized that this increase in nCLB with CBD use may explain some of the increased anti-epileptic effects when these medications are combined.[64] As CLB is not known to be hepatotoxic, increasing levels of nCLB are unlikely to explain the elevated LEs seen in these participants.

Many other AEDs have the potential to cause a DILI,[67] but these medications were rarely reported to be taken by the participants on CBD who sustained a DILI, and if present, they were co-administered with VPA and/or CLB.[2]

Several studies that assessed CBD-related LE elevations allowed the use of less than 2 g/day of acetaminophen (paracetamol), a drug known to cause dose-dependent hepatocellular LE elevations and DILI.[29,43,49] Out of the four participants who took concomitant acetaminophen, one had predominantly cholestatic pattern of LE elevation (not consistent with acetaminophen-induced DILI), and two out of four only took one dose (500 mg in one, 1000 mg in the other), making it an unlikely contributor to their LE elevation.[2,29,43,68]

Some studies that assessed CBD-related LE elevations allowed the use of hormonal birth control, which has been linked to elevation of cholestatic LEs.[29,49,56,68] At least two participants with DILI in these studies were taking concomitant hormonal birth control, but both had a hepatocellular pattern of LE elevation, less consistent with estrogens' impact on LEs.[56,68]

Although concomitant medications, particularly VPA, appear to be a risk factor for CBD-associated hepatotoxicity, it does not entirely explain the phenomena. There are several cases of healthy adults taking CBD who developed clinically significant LE elevations while not taking any other medication.[48,56]

Genetics. The role of genetics should be further investigated and likely contributes some magnitude of risk. A study on pharmacogenetic predictors of CBD response and tolerability in epilepsy observed the genetic variant ABCC5 rs3749442 was associated with a lower likelihood of abnormal liver function tests.[69] Similarly, individual risk of DILI from other offending agents has been associated with genetic differences in HLA alleles and mitochondrial function.[37,44] While this currently may be less clinically relevant due to the infrequent use of genetic testing in normal clinical practice, it does support the idea that clinicians should be aware some individuals may be at a lower or higher risk of liver injury at baseline, irrespective of other risk factors.

Abnormal baseline liver enzymes. Evidence from Epidiolex® (a high-concentration oral CBD oil) trials support that baseline

transaminase levels above the ULN is a risk factor for further LE elevations when taking CBD.[55,60] Similar findings were reported in a recent meta-analysis on CBD-associated hepatotoxicity.[2] Only a small number of CBD trials which monitored LEs reported individual participants' baseline LEs. Of the trials that did, 13/27 cases (48.15%) of CBD-associated LE elevations and 5/12 cases (41.67%) of DILI occurred in individuals with baseline LE elevations between 1 and 3 × ULN.[29,47,66,70,71] Within said trials, LE elevations were detected in participants primarily taking moderate to high doses of CBD, within the first 30 days of treatment. Conversely, others have reported a participant with baseline LE elevation that did not progress to clinically significant elevations after CBD initiation.[72] If initiating CBD, those with abnormal LEs at baseline should be closely monitored for DILI.

History of chronic liver disease. Investigation on the impact of CBD in those with chronic liver disease has yielded limited but interesting results. Preclinical findings suggest that CBD may have therapeutic benefits in the management of chronic liver diseases, including metabolic dysfunction-associated steatotic liver disease (MASLD), metabolic dysfunction-associated steatohepatitis, alcohol-associated liver disease (ALD), chemical liver injury, and hepatitis-C-virus-induced liver fibrosis, potentially due to its anti-inflammatory and antioxidant effects.[10,13,51–53,73,74] Mouse models of MASLD and ALD have shown that CBD reduces nuclear factor kappa-light-chain-enhancer of activated B cells activation, reducing the development/progression of steatosis.[70] Further, in mouse models of non-alcoholic liver fibrosis, CBD decreased the infiltration of T-cells and macrophages, reduced the migration of fibroblasts through impedance of transforming growth factor-β and IL-4, and suppressed transcription of collagen synthesizing genes, reducing fibrosis.[70] Additionally, CBD, through transient receptor potential channels (TRPs) activation and restoration of PPARα protein expression, is involved in the regulation glucose homeostasis, preventing lipid accumulation and insulin resistance in the liver.[10] Overall, these preclinical trials show that CBD, through its interactions with various receptors including CB1, CB2, TRPs, PPARs, and GPR55, has a potential protective effect against chemical, viral, and metabolic hepatotoxicity through the inhibition of oxidative stress, reduction of T-cell and macrophage infiltration, prevention of fibrosis, and maintenance of metabolic homeostasis.[13]

While evidence in humans is more limited, one study in patients with autoimmune hepatitis found that CBD use was associated with self-reported improvement in extrahepatic symptoms.[75] Another study found that the consumption of cannabis was associated with reduced incidence of liver disease and improvement in liver disease outcomes among those with chronic hepatitis C infection, suggested to be due to the effects of CBD.[76] While much of this evidence is low in quality and does not report CBD dose or duration, it does highlight an interesting area of future research.

Age. Age was not found to be a significant risk factor for CBD-associated DILI, although the current literature is primarily in populations under 50 years of age and may not be translatable to older populations.[2] The current evidence of CBD-related hepatotoxicity in older populations (> 65 years) is limited. Further research in this population is warranted due to increasing CBD consumption within this group.

Clinical presentation and time course. Many people who develop CBD-associated hepatotoxicity appear to be asymptomatic, confounded by inconsistent or a lack of symptom reporting in many clinical trials.[2] Figure 1 reviews the most commonly reported clinical presentations of CBD-associated hepatotoxicity. None of the current CBD studies reported the symptoms of severe hepatotoxicity (anorexia, jaundice, pale stools, and/or dark urine).

Rash (macular, papular, erythematous, or follicular) was seen in a significant portion of participants (11.7%) in one study when

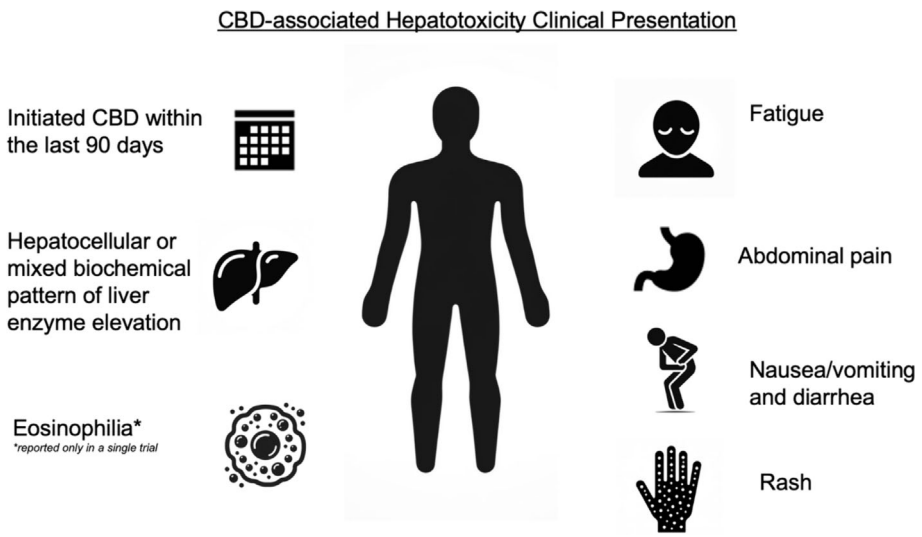

Figure 1 Common clinical presentation of cannabidiol-associated livery injury. Data gathered from Lo *et al.* (2021) review. Symptoms were not associated with dose and in many cases (especially in pediatric studies) the participants were asymptomatic.

very high dose oral CBD was rapidly initiated (e.g., starting at 1500 mg total daily dose) but was rarely seen with a slower titration schedule.[2,57] This may indicate a potential impact on the rate of dose titration and the CBD formulation.[57] Mild rashes were monitored, but moderate to severe rashes prompted discontinuation of CBD.[57] Liver injury associated with eosinophilia and rash is suggestive of a severe immunoallergic reaction and investigations should be undertaken to rule out internal organ involvement as can be seen with drug reaction with eosinophilia and systemic symptoms (DRESS).[32]

The biochemical pattern of CBD-associated DILI is entirely hepatocellular in the pediatric studies, where a small number of participants in adult studies showed a mixed pattern, with ALP $>$ 2 $\times$ ULN.[2,29,43,49]

Evidence suggests that LE elevations are most likely to occur during the initiation phase of CBD. In the included trials of a recent meta-analysis, the time to detection was within the first 5 weeks of initiation.[2] The FDA/Epidiolex® prescriber information reported that most LE elevations occurred within the first 30–90 days of CBD initiation, although rare cases have been observed up to 18 months after CBD initiation, particularly in those taking concomitant VPA.[40,55,60]

Prognosis. Despite the frequent findings of elevated LEs and DILI with CBD use, no severe cases of DILI have been reported, as determined by Hy's law (serum ALT $>$ 3 ULN, ALP $<$ 2 ULN, and total bilirubin $>$ 2 ULN).[2,77,78] Almost all participants who sustained CBD-associated DILI had CBD discontinued, and the majority of cases were reported as resolved, with only 2/47 cases (3.45%) reported as unresolved at the time monitoring ended.[2] In these two cases, the degree of LE elevation was unclear at the conclusion of the monitoring period.

Most cases (128/159, 80.50%) of CBD-associated LE elevations $\geq$ 3 $\times$ ULN were reported as resolved.[2] Of these resolved cases, 64/128 (50.00%) had CBD discontinued, in 32/128 cases (25.00%) LEs resolved spontaneously with continued CBD use, 21/128 cases (16.40%) LEs resolved with a dose reduction of other AEDs, 2/128 cases (1.56%) LEs resolved with dose reduction of CBD, and 9/128 cases (7.03%) LEs resolved with unclear reasons provided (either cessation or dose reduction of CBD or AEDs). Seven of 159 cases (4.40%) were reported as unresolved at the time monitoring ended, and the outcome was unclear for 24/159 cases (15.09%).[46,79,80]

Findings support that most CBD-associated LE elevations and DILI resolve within 2 weeks to 4 months following CBD dose reduction or discontinuation, or decreasing the dose of other hepatotoxic medications.[2] A portion of those (25%) may resolve with no adjustments and continued use of CBD and other therapies.

Given trial protocols, the majority of participants with elevated LEs stopped CBD or reduced the dose of CBD or other hepatotoxic drugs. Thus, it is unknown how many participants would have had their LEs spontaneously resolve if they had continued the same dose of CBD, or if any participants would have progressed to acute liver failure. This is an important discussion point, as those who take non-prescription CBD without the support of a healthcare provider are unlikely to have their LEs monitored and many may not report their use to their HCP. Trial duration and withdrawal criteria also inhibit the ability to assess if there is a risk of progression to chronic liver disease in those with CBD-associated hepatotoxicity.

Considerations of the current evidence and limitations. The FDA[35] has recommended different biochemical and clinical guidelines for DILI in pharmaceutical research, where discontinuation of treatment should be considered for any of the following:

1. ALT or AST $>$ 8 times the ULN
2. ALT or AST $>$ 5 times the ULN sustained over 2 weeks
3. ALT or AST $>$ 3 times the ULN and bilirubin $>$ 2 times the ULN or INR $>$ 1.5
4. ALT or AST $>$ 3 times the ULN with eosinophilia ($>$ 5% total white blood cell count) or symptoms (nausea, vomiting, fatigue, right upper quadrant abdominal pain, fever, rash).

The biochemical criteria for DILI requiring drug discontinuation in clinical trials are more liberal than the clinical criteria used by the AASLD.[27,34] As participants in clinical trials are often receiving more monitoring than would be completed in the real world, there is a higher likelihood of finding spurious abnormal lab results. The goal of this more liberal criteria in clinical trials is to monitor participants with elevated LE for resolution despite drug continuation, termed clinical adaptation (transient LE elevation not associated with liver damage), that would likely go unnoticed in the real world. Benign and transient LE elevations would not be recognized if participants were removed from trials prematurely (once meeting the clinical DILI criteria), potentially leading to the rejection of promising medications based on a false association with hepatotoxicity. The FDA reports that these guidelines have not been systematically or prospectively evaluated but are often used in practice.[35]

This difference in the definition of DILI in clinical work and pharmaceutical research poses several challenges. When assessing studies retrospectively, many will state that no participant sustained a DILI, despite many participants meeting the biochemical and/or clinical criteria for DILI proposed by the AASLD.[2,27] Complicating this issue is the inconsistent reporting of follow-up laboratory work on participants with significant LE elevations who were not perceived as having a DILI based on the more liberal research withdrawal criteria.

As LEs can rise and fall in days and symptoms can be delayed after biochemical evidence of DILI, it is crucial to repeat the elevated LE measures within 48–72 h, especially if aminotransferases are $>$ 3 $\times$ ULN or ALP $>$ 1 $\times$ ULN, to determine the trend and peak levels.[32,35] Clinical trials that do not conduct and/or report frequent, participant-specific laboratory monitoring in those with elevated LEs create the potential risk of a participant sustaining a serious liver injury if the drug was continued and underreporting the rate of DILI.

Another limitation in assessing the rate of DILI in these trials is that many will report symptoms (fatigue, nausea, vomiting, etc.) and the number of participants with elevated LEs as a ratio or average of the whole, making it challenging to connect the participants with both symptoms and elevated LE. This could be mitigated by offering participant-specific data. Further research

that allows for the evaluation of DILI using clinical definitions is important for real-world applicability.

It is important to note that there is a lack of data on hepatotoxicity with non-medical and/or unregulated CBD use. Many CBD health products are not regulated to the same degree as pharmaceutical CBD products, making it difficult to ascertain the exact CBD content of a product.[81–83] This increases the likelihood of inaccurate CBD dosing, as there has been evidence of batch level differences of CBD content within the same product.[81–84] Further, the lack of HCP oversight with self-use CBD, leads to inherent challenges with LE monitoring. As such, for individuals taking non-prescription CBD, a lack of education on dosing and associated risks, the variability in CBD content in different products, the availability of highly concentrated CBD products, and hesitancies in reporting CBD use due to stigma, may lead to an increased risk of liver injury. In an ideal world, this clinical framework could be applied to those utilizing non-prescription CBD formulations in conjunction with the individual's HCP.

Diagnosis and management of CBD-associated hepatotoxicity

Diagnosis of CBD-associated hepatotoxicity. Whether an individual is initiating CBD or presents to primary care with suspected DILI, the steps to diagnose CBD-associated DILI can be completed following a step-wise approach (Fig. 2), based off of the framework presented in the ACG and AASLD guidelines.[27,77]

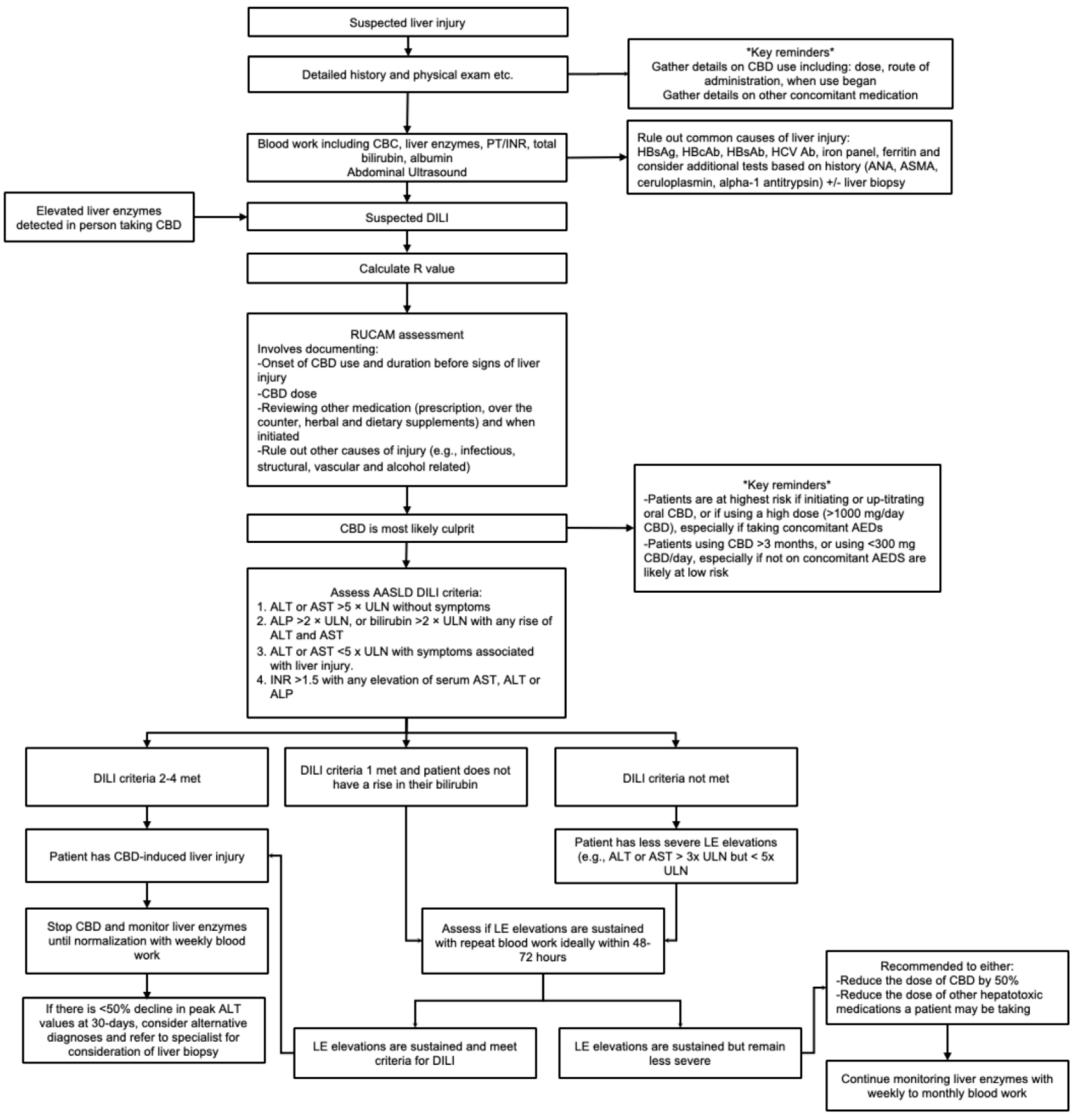

Figure 2 Framework for diagnosis and management of CBD-associated DILI. Information adapted from.[13,26,27] Abbreviations: AASLD, American Association for the Study of Liver Diseases; AEDs, anti-epileptic drugs; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; CBD, cannabidiol; CBC, complete blood count; DILI, drug-induced liver injury; INR, international normalized ratio; LE, liver enzymes; PT, prothrombin time test; RUCAM, Roussel Uclaf Causality Assessment Method; ULN, upper limit of normal.

CBD-associated DILI is both a clinical and biochemical diagnosis. Diagnosis involves an exclusionary approach based on a detailed history, blood work, imaging, and potential liver biopsy. A comprehensive history should be taken, including the assessment of host, environmental, and drug-related risk factors. Blood work, including LEs (ALT, AST, ALP, and GGT) and LFTs should be completed in addition to serology to rule out other common causes of liver injury (hepatitis serologies etc.). Exclusion of competing etiologies of liver injury is a key aspect of diagnosis.[37] Vuppalanchi and Ghabril[37] provide a useful framework if abnormal LEs and/or LFTs are found by asking the four questions:

1. Is there underlying liver disease?
2. Is there competing etiology?
3. Is this DILI?
4. How do I manage it?

They also provide guidance outlining the potential blood tests and imaging studies to consider when evaluating unexplained LE elevation and recommendations for using *R* value for evaluation of a case of suspected DILI. If DILI is being considered, an *R* value should be calculated (Table 3).

Causality assessments using validated tools such as RUCAM are recommended to help delineate if CBD is the most likely culprit for the underlying liver injury.[26,37,68] This involves documenting the onset of CBD use and the duration of use before diagnosis of liver injury, the dose of CBD, and ruling out other common causes of liver injury, including infectious, structural, vascular, and alcohol-related liver injury. A review of the individual's other medications (prescription, over-the-counter), herbal and dietary supplements and when they were initiated is prudent. Scoring systems should not be used in isolation for the diagnosis of DILI but are helpful in the diagnostic framework to exclude competing etiologies for liver injury. If there is ongoing uncertainty, it is recommended that clinicians seek expert consultation.[26]

The following biochemical parameters laid out by the AASLD guidelines are supportive of a DILI diagnosis[27,85]:

1. ALT **OR** AST $> 5 \times$ ULN without symptoms on two separate occasions at least 24 h apart
2. ALP $> 2 \times$ ULN, **OR** bilirubin $> 2 \times$ ULN with any rise of ALT and AST
3. ALT **OR** AST $< 5 \times$ ULN with symptoms associated with liver injury.
4. INR > 1.5 with any elevation of serum AST, ALT, or ALP.

Clinicians should keep in mind that people are at the highest risk if they are initiating or up-titrating CBD, or if they are using a high dose, especially if they are taking concomitant AEDs.

People who have been using CBD for over 3 months and using low-dose CBD day are unlikely to have a CBD-associated liver injury, especially if they are not taking concomitant AEDs. If a person is taking concomitant AEDs and taking CBD ≥ 300 mg, LEs should be monitored every 2 weeks for the first 6 weeks, then monthly for the first 6 months.[55,60,86] Management and follow-up depend on the individual patient and the outcome of the diagnostic investigations.

Management of CBD-associated hepatotoxicity.

Management of CBD-associated hepatotoxicity depends on whether a person meets criteria for DILI or if they have LE elevations below the threshold of DILI. As per ACG/AASLD guidelines, CBD should be discontinued in any person with DILI, and

Table 4 Liver injury prevention and mitigation strategies in people initiating CBD

Assess baseline LEs and LFTs
• Especially important in those at higher risk of CBD-associated hepatotoxicity
– Taking concomitant known hepatotoxic drugs (especially VPA)
– Having history of minor elevations in baseline aminotransferase ($< 3 \times$ ULN)
• CBD is not recommended to be initiated if baseline aminotransferases are elevated $> 3 \times$ ULN without specialist evaluation
Follow a low dose slow titration regimen
• A "start low, go slow" approach is recommended with the administration of cannabinoids
• More rapid titrations have been associated with immunological reactions and hepatotoxicity[88]
– Consider starting oral CBD at a dose of 10–25 mg/day based on the individual patient and indication[88]
– It is recommended that for oral CBD formulations, when used in seizure disorders, the dose should be increased no more frequently than weekly[40,60,88]
– It is recommended that for oral CBD formulations, when used in other indications, the dose should be increased no more frequently than every 2 days[88]
Monitor for symptoms and LE elevation
• People and their families at risk should be informed of the symptoms associated with hepatotoxicity (Fig. 1) and the importance of regular monitoring to mitigate risk
• If new symptoms arise, people should contact their HCP and hold CBD until urgent blood work (LEs, INR, bilirubin) is completed
• If not at increased risk of hepatotoxicity and taking ≥ 300 mg of CBD, monitor serum aminotransferases, ALP, INR, and total bilirubin levels at 1, 3, and 6 months after CBD initiation
• If people are at higher risk of CBD-associated hepatotoxicity and taking ≥ 300 mg of CBD, monitor serum aminotransferases, ALP, INR, and total bilirubin levels biweekly for the first 6 weeks, then monthly until 6 months post-CBD initiation
Based on current evidence, avoidance of utilizing moderate to high doses of CBD appears to be the safest strategy for preventing liver injury

ALP, alkaline phosphatase; CBD, cannabidiol; INR, international normalized ratio; LE, liver enzymes; LFT, liver function tests; ULN, upper limit of normal.

certainly in any person with severe DILI as denoted by Hy's law (serum ALT > 3 ULN, ALP < 2 ULN, and total bilirubin > 2 ULN).[26,27,60] Those meeting these criteria are at higher risk of mortality from acute liver failure or requiring liver transplantation.[55,78,87] The one exception may be if the person has elevated aminotransferases (ALT or AST > 5 × ULN), is asymptomatic, and does not have a rise in their ALP, bilirubin, or INR. In this situation, repeat blood work, ideally separated by 48–72 h, should be completed to assess if the elevation in aminotransferases is sustained, or if this is a transient or spurious result. If aminotransferases remain > 5 × ULN, this is further biochemical evidence of a DILI, and CBD should be discontinued. If CBD is discontinued, aminotransferases should continue to be monitored weekly until resolution.[28] If aminotransferases do not reduce by 50% 30 days after CBD discontinuation, alternative diagnoses should be considered and referral to appropriate specialists is recommended.

If LE elevations are less severe (ALT or AST > 3 × ULN but < 5 × ULN **OR** ALP > 1 × ULN but < 2 × ULN), it is recommended to either reduce the dose of CBD or reduce the dose of other hepatotoxic medications a person may be taking. This decision will be person-dependent, including an analysis of which medication (CBD *vs* other hepatotoxic medication) is more therapeutically beneficial. LEs, INR, and bilirubin should continue to be monitored biweekly to monthly to ensure that aminotransferases continue to decrease and normalize.

Prevention and mitigation strategies. Based on the current literature, several recommendations can be made to reduce the risk of CBD-associated hepatotoxicity (Table 4). In people initiating CBD, we recommend assessing baseline LEs and liver function tests. If increasing the dose of CBD ≥ 300 mg, serum aminotransferases, ALP, INR, and total bilirubin levels should be assessed at 1, 3, and 6 months after CBD initiation.[60,86] If people present with minor baseline LE elevations (< 3 × ULN) or are taking other known hepatotoxic drugs, especially VPA, more frequent monitoring within the first month is recommended (Table 4). While taking CBD, if any new symptoms associated with hepatotoxicity arise (Fig. 1), CBD should be stopped until urgent blood work to assess LEs, INR, and bilirubin is completed. The management of CBD-associated LE elevations is described in the Management of CBD-associated hepatotoxicity section and Figure 2.

Conclusions

There is an association between the use of CBD and LE elevations/DILI, particularly at moderate to high doses of CBD. With the increasing use of CBD, all HCPs should be aware of this potential adverse drug reaction, which meets the CIOMS classification of a common adverse drug reaction. There is a lack of clinical recommendations for how to assess and manage this adverse drug reaction. People utilizing cannabis containing CBD ≥ 300 mg are recommended to have serum aminotransferases, ALP, INR, and total bilirubin levels measured, particularly during the first 6 months of use. People taking CBD ≥ 300 mg with mildly elevated baseline aminotransferases (< 3 × ULN) or those taking concomitant medications that may be hepatotoxic should be more closely monitored. Management approaches include reduction of CBD dosage, reduction of the dose of other hepatotoxic medications, or stopping CBD use. Information available on this topic remains limited. The current recommendations are meant to help guide clinicians but should always be considered in constellation with emerging evidence and clinical judgment. More research and improved reporting standards are crucial to accurately gauge the prevalence of elevated LEs and DILI in a diverse range of patients using CBD. Using novel tools such as the DILI causality assessment tool (DILI-CAT),[89] which uses drug-specific liver injury phenotypes to compute a scoring algorithm to examine a drug's potential hepatotoxicity may be a worthy endeavor. Moving forward, it is essential to better examine risk factors for CBD-associated hepatotoxicity and to establish best practices for management through more rigorous research.

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