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Review Article

"*Is medical cannabis safe for my patients?*" A practical review of cannabis safety considerations

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ABSTRACT

Medical cannabis use is increasing worldwide. Clinicians are commonly asked by patients to provide guidance on its safety and efficacy. Although there has been an increase in research on the role of medical cannabis for a number of different conditions, we found that there was a paucity of clear safety guidance on its use. We aim to address this issue by answering two pertinent clinician safety questions:

1 Can medical cannabis be safely used in this patient?
2. What strategies can be used to ensure that any harms from medical cannabis are mitigated?

To address these questions, we reviewed available evidence and provided expert clinical opinion to summarize the fundamental components for evaluating medical cannabis safety and strategies to reduce risk from its use. Our review resulted in a safety-focused framework for medical cannabis initiation and utilization. We provide clear recommendations for patients being considered for cannabis (e.g. precautions, contraindications and drug interactions). Risk mitigation strategies such as appropriate chemovar (strain) selection, routes of administration, and dosing are reviewed. As with any other pharmacotherapy, we review the key components of monitoring and address potential issues that may arise while using medical cannabis. We propose a structured assessment and monitoring strategy that can be used by clinicians recommending cannabis (CRC) to guide patients through each step of their cannabis journey. This framework can be used to ensure that medical cannabis utilization is associated with the lowest possible risk to the patient.

1. Introduction

The use of cannabis for medical purposes is increasing worldwide [5,32]. With the changing public and political opinion, more countries are implementing medical cannabis legalization. Although approved in many regions, safety data from clinical trials are not as robust for medical cannabis as for other pharmacotherapies. The focus of this piece will be on herbal medical cannabis, not pharmaceutical cannabis-based medicines (e.g. Sativex, Nabilone, Dronabinol), as the safety considerations for herbal cannabis are less clear in the current literature. However, many of the considerations presented below can be applied to both.

Data from Health Canada showed that the majority of people (73%) reporting cannabis use for medical purposes did not have a government authorization for its use, and were acquiring their cannabis through non-medical sources [15]. The lack of healthcare professional (HCP) guidance can be problematic in medically complex patients, particularly those with chronic conditions and polypharmacy.

Here, we summarize safety considerations for patients being considered for medical cannabis. Although some HCPs do not support the use of medical cannabis based on current evidence, many patients will use cannabis to improve their symptoms. It is important for each HCP to be able to assess cannabis safety for any patient using from legal or illicit sources.

With respect to safety, we answer two fundamental questions:

- Can medical cannabis be used safely in this patient?

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- What strategies can be used to ensure that any harms from medical cannabis are mitigated?

2. Considerations for initiating and titrating medical cannabis

When initiating a patient on medical cannabis a host of factors should be considered (Fig. 1). Prior to cannabis initiation, clinicians recommending cannabis (CRC) should screen for potential precautions, contraindications, and drug interactions (Tables 1 and 2). Further, we encourage the use of validated questionnaires such as General Anxiety Disorder-7 (GAD-7), Patient Health Questionnaire-9 (PHQ-9), and Brief Pain Inventory (BPI), as these tools can help clinicians to monitor response to therapy and evaluate the risk versus benefit during follow-up.

After assessing potential precautions, contraindications, and drugs interactions, clinicians should weigh the overall risk vs benefit of medical cannabis use in each patient. Each of these factors could influence the process of initiation and titration. Route of administration and chemovar (strain) selection should be considered taking into account the individual patients safety considerations (Table 3). Following selection, a low-dose, slow titration strategy should be encouraged (Table 4). Each patient will commonly require an individualized approach.

The risks and benefits of cannabis should be assessed for each patient. Clinicians should screen for the following considerations and comorbidities that may influence patient safety (Table 1).

2.1. Screen for precautions and contraindications (Step 1)

2.1.1. Considerations

Immunocompromised. Cannabis has the potential of being contaminated with microorganisms. Patients who are immunocompromised (due to a health condition or immunomodulating medications) have a higher infection risk when exposed to contaminated cannabis [42]. Cannabis products from a regulated source are always preferred for these patients. Many immunocompromised patients take medications that may interact with cannabis. Caution should be taken when used with a calcineurin inhibitor (e.g. tacrolimus) as CBD may increase toxicity (See *Drug interactions* section) [3, 4]. CBD may also worsen the efficacy of programmed cell death protein 1 (PD1) inhibitors, also known as immune checkpoint inhibitors [60]. There is preliminary evidence THC could inhibit the proliferation of lymphocytes and suppress CD8 T-cell and cytotoxic T lymphocyte cytolytic activity [7,38]. As such, both CBD and THC could potentially interfere with immunotherapy in cancer patients. Interactions between monoclonal antibody therapies (e.g. TNF-alpha inhibitors) and cannabis are unlikely, although it is important to note that no formal drug interaction trials have yet to be completed.

Chronic kidney disease. Cannabinoids are thought to be safe in patients with chronic kidney disease (CKD), including end stage renal disease; monitoring of renal function may be helpful [51,52]. Clinicians should recommend using the lowest effective dose, and abstaining from illicit

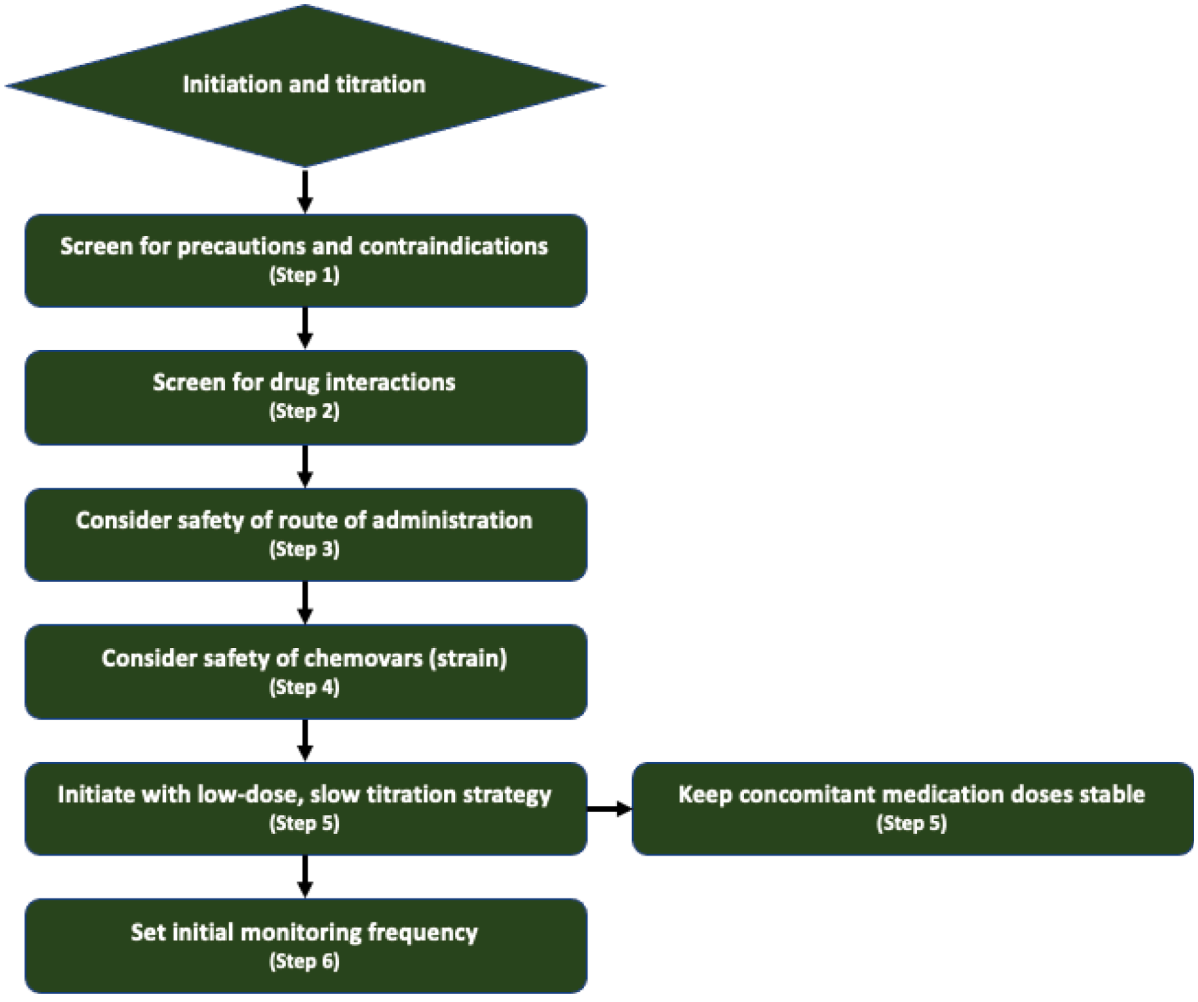

Fig. 1. Key considerations when initiating and titrating medical cannabis.

Table 1
Precautions and Contraindications.

Considerations[A]	Precautions[B]	Relative Contraindications[C]	Contraindications[D]*
Immunocompromised Chronic Kidney Disease Older adults Patients with concurrent medical conditions Polypharmacy Potential drug interactions	Concurrent mood or anxiety disorder Have risk factors for cardiovascular disease Tobacco use E-cigarette use Severe liver dysfunction /disease Medications associated with sedation or cognitive impairment Driving or safety sensitive occupations	Under 25 years of age Current or past cannabis use disorder Current or past substance use disorder	Unstable cardiovascular disease Respiratory disease (if smoking cannabis) Personal or strong family history of psychosis/ bipolar Pregnant, planning on becoming pregnant, or breastfeeding

* If it is deemed there may be a benefit, clinicians should consider referral to a specialty, and experienced clinician recommending cannabis, to ensure the appropriateness of this therapy.© Caroline MacCallum, MD, 2021; used with permission. Information gathered from [34,49,75].

Table 2
Potential Cannabinoid Drug Interactions*

Enzyme	Interaction and effect	Drugs
CYP 3A4	**Inducers:** may decrease THC and/or CBD **Inhibitors:** may increase THC and/or CBD **Substrates:** CBD is potential inhibitor of CYP3A4 and could increase 3A4 substrates. Caution with medications with smaller therapeutic index (e.g. tacrolimus). Unlikely to have effect on THC	Carbamazepine, phenobarbital, phenytoin, rifampin, St. John's wort Azole antifungals, clarithromycin, diltiazem, erythromycin, grapefruit, HIV protease inhibitors, macrolides, mifepristone, verapamil Alprazolam, atorvastatin, carbamazepine, clobazam, cyclosporine, diltiazem, HIV protease inhibitors, buprenorphine, tacrolimus, cyclosporine, phenytoin, sildenafil, simvastatin, sirolimus, verapamil, zopiclone
CYP 2C9	**Inducers:** may decrease THC concentration. Unlikely to have effect on CBD **Inhibitors:** may increase THC concentration. Unlikely to have effect on CBD **Substrates:** THC and/or CBD may increase drug levels, should monitor for toxicity	Amiodarone, fluconazole, fluoxetine, metronidazole, valproic acid, sulfamethoxazole Carbamazepine, rifampin Warfarin, rosuvastatin, phenytoin
CYP 2C19	**Inducers:** may decrease CBD and THC **Inhibitors**: may increase CBD and THC **Substrates:** CBD may increase the level of medications metabolized by 2C19 such as norclobazam (active metabolite in clobazam). CBD may also prevent clopidogrel from being activated. Unlikely to have effect on THC	Carbamazepine, rifampin, St. John's wort cimetidine, omeprazole, esomeprazole, ticlopidine, fluconazole, fluoxetine, isoniazid aripiprazole, citalopram, clopidogrel, diazepam, escitalopram, moclobemide, norclobazam, omeprazole, pantoprazole, sertraline
CYP 1A1 and 1A2	**Substrates:** Smoking cannabis can stimulate these isoenzymes and increase the metabolism of these. medications.	Amitriptyline, caffeine, clozapine, duloxetine, estrogens, fluvoxamine, imipramine, melatonin, mirtazapine, olanzapine, theophylline
p-glycoprotein	**Substrates:** CBD may inhibit p-glycoprotein drug transport. Should monitor for toxicity. No effect from use of THC	Dabigatran, digoxin, loperamide

* Formal drug interaction studies with cannabinoids have not been conducted. Other drug interactions are possible as more individuals use cannabinoids with other medications.© Caroline MacCallum, MD, 2021; used with permission. Information gathered from [3,4,14,16,26,34,44,53,74].

cannabis sources, as they may be contaminated with heavy metals, pesticides, and solvents, which may increase toxicity in people with CKD [51,52]. Smoked cannabis should be avoided in case of cardiorenal effects [51].

Older adults. Cannabinoids are considered by some clinicians for older adults with a poor response to other treatments [1,2,44,47]. The physiological changes with aging (e.g. decreased organ function, impaired cognitive function, decreased fat-free body mass) may increase the risk or magnitude of adverse and impairing effects related to cannabis consumption [1,2,47]. Typically, there is a greater risk for drug interactions in this population [1,2,13]. This population normally requires more frequent monitoring [47]. To mitigate the risk of adverse events a low dose, slow titration regime should be employed (See *Initiate with low-dose, slow titration strategy* section).

Concurrent medical conditions and polypharmacy. CRCs should be aware of conditions which may compound impairment; and also evaluate for risk of drug interactions (Tables 1 & 2). There are limited studies evaluating the safety of cannabis use in people with comorbid diseases [2,8,20,55]. Sedating effects may be compounded with certain conditions or concomitant medications (See *Drug Interactions* section). Patients with health conditions should be monitored more frequently for changes in their health status (See *Follow up* Potential Drug Interactions).

Potential drug interactions. Please see Screen for drug interactions (Step 2) for more information.

2.1.2. Precautions

Concurrent active mood or anxiety disorder. While a causal relationship between cannabis use and mental health disorders has not been established; there is evidence that a relationship exists and therefore precautions should be taken [64]. The strongest evidence for the negative impact of cannabis use on mental health is within recreational populations and is associated with an early age of initiation and exposure to large doses of THC [28]. There is data showing that individuals with depression, anxiety, and post-traumatic stress disorder (PTSD) are more likely to use medical cannabis [12,37,39,62]. However, the directionality in these populations remains unclear. If cannabis is being considered for these patients, clinicians should consider CBD dominant products with more frequent monitoring [43]. Some conditions (e.g. psychosis and bipolar disorder) pose a more serious risk, and cannabis is generally contraindicated (*more information in contraindication section below*).

Have risk factors for cardiovascular disease. Please see Unstable cardiovascular disease section for more information.

Tobacco use. Tobacco use is a well-known risk factor for cardiovascular

Table 3
Recommendations for initial route of administration and strain selection.[a]

Route of Administration	Strain Selection	Appropriate Patient Population
Oral Oil or Capsules	Based on safety concerns for the following patient populations, consider initiating with a CBD dominant product: ◦ Older adults ◦ <25 years of age ◦ History of mental health ◦ Heart conditions ◦ Personal or strong family history of psychosis/ bipolar ◦ Concurrent mood or anxiety disorder ◦ Severe liver disease ◦ Other conditions or medication regime associated with sedation or cognitive impairment (may compound effects of THC) ◦ Individuals in safety-sensitive occupations ◦ Polypharmacy ◦ At risk for pharmacodynamic drug interactions*	**Recommended for most patients with chronic symptoms** Strongly recommended for patients with or at risk for respiratory disease
Vaporization**	Clinicians should assess risk vs benefit for using different cannabis chemovars by this route.	Recommend for patients requiring rapid onset of action • Migraines • Nausea • Acute pain • Appetite • Initiation of sleep Generally, not recommended for patients with respiratory disease
Other dosage forms (eg sprays, suppositories, topicals, edibles)	There is insufficient evidence on safety to make recommendations for these dosage forms	

* slower initiation and more frequent monitoring are recommended in patients with known drug interaction such as with clobazam, cyclosporin, warfarin etc.
** We recommend vaporization of dried cannabis flower, in some regions there are THC containing e-cigarettes or vape pens available but we cannot make safety recommendations based on limited data*Clinicians are recommended to adjust these recommendations based on the product availability in their region*
[a] Clinicians are recommended to adjust these recommendations based on the product availability in their region.

disease (CVD) and respiratory disorders. A patient who smokes tobacco may be more likely to smoke their cannabis, or add tobacco to their cannabis, potentially elevating the risk of CVD and respiratory disorders. Nicotine dependence has not been shown to cause a greater risk of developing problematic cannabis use [49]. In patients who use tobacco, oral cannabis would be considered the safer dosage form.

Electronic cigarette (Vape Pen) use. In recent years, there has been an increase in the incidence of E-Cigarette, or Vaping Product Use-Associated Lung Injury (EVALI). The use of both nicotine vape pens and cannabis vape pens has been linked to severe respiratory illness (Layden et al., 2019). A proportion of these cases have reported the use of THC containing vaping products, most commonly obtained from unregulated, illicit sources [40]. Accordingly, the CDC recommends not using e-cigarette, or vaping products obtained from illicit sources [17]. Vitamin E acetate has been strongly linked to EVALI, however, evidence isn't sufficient to rule out other chemicals as well ([10]; Centers for Disease Control and Prevention [17]. There is no strong evidence that vaporization with dried cannabis flower increases the risk of EVALI.

Severe liver dysfunction. Severe liver dysfunction may affect the metabolism of cannabis. A cautious approach should be taken with dosing, in addition to more frequent monitoring (See *Initiation with low-dose, slow titration strategy* (Step 5) & *Follow up* section). In general,

Table 4
Low-dose, slow titration strategy*

Step	Oil	Vaporization**
Step 1	Start with 5 mg CBD oil BID	Start with one inhalation
Step 2	Titrate dose by 5 mg CBD every 2-3 days (if no adverse events or until patient reaches goals of therapy)	Wait 15-30 minutes
Step 3	THC: If CBD alone is not reaching treatment goals, clinicians can consider adding THC after assessment of the benefit vs risk (see Appendix 1, Table C). Recommended starting dose is 1- 2.5 mg THC at bedtime. Titrate by 1-2.5mg THC every 2-7 days If daytime THC is needed, starting dose is 1 mg THC. Titrate by 1-2.5mg THC every 2-7 days.	Increase by 1 inhalation every 15-30 minutes until patient reached goals of therapy (providing no adverse events)
Step 4	Doses above 40 mg/day of THC are rarely required if reached, clinicians should re-assess risk-benefit ratio for patient	Final dose = total consecutive inhalation doses within a dosing session required to reach goals of therapy

Information gathered from [44,76].
* Dosing and tolerability are highly patient specific if a clinician's wishes to use a lower dose, and or a slower titration this could also be considered.
** For strain selection see Table 3

there is no strong evidence between cannabis use and progression of pre-existing liver disease [49]. One exception where there is some conflicting data is on the association between cannabis and liver fibrosis in those with viral hepatitis C (HCV) [34,71]. However, a more recent longitudinal study and a review on the health effects of cannabis, concluded that there does not appear to be an association between progression of liver fibrosis or hepatic disease and cannabis use in individuals with HCV [49,72].

Medications association with sedation and cognitive impairment. Please see *Concurrent medical conditions and polypharmacy* section for more information.

Driving or safety sensitive occupations. Cannabis can lead to impairment in multiple neurocognitive and psychomotor domains [22]. Evidence suggests the predominant impact of cannabis on impairment is mostly due to THC [22]. In patients who work in safety sensitive occupations, defined as one "in which incapacity due to impairment could result in direct and significant risk of injury to the employee, others or the environment" [3,23] , or partake in safety-sensitive activities like driving, risk of impairment is an important consideration. It is generally recommended patients using THC should not drive or engage in safety-sensitive activities for at least 4 hours after inhalation, 6 hours after oral ingestion, or 8 hours, if euphoria is experienced [22,29,44]. . There is an increasing body of evidence supporting that daily medical cannabis users tend to be more tolerant to the impairing effects of THC [22,66,69,70]. It has previously been demonstrated that at a dose of 0.5 mg/kg THC, daily users did not display acute impairment on most neurocognitive impairment tasks, except for a decrease in impulse control at high THC concentrations (>10 ng/ml) [66]. A review of the duration of impairment found that within 4 hours after THC inhalation, and 6-8 hours if ingestd orally, medical cannabis users were no longer impaired [22]. In contrast, a recent RCT showed that following CBD inhalation of 13.75 mg there was no indiction of neurocognitive impairment, including for measures of driving performance [68]. Another study investigating even higher doses of CBD (100mg oral and vaporized) also observed no cognitive or psychomotor impairments [67]. This is particularly relevant for medical cannabis users, who commonly use CBD in the daytime to control symptoms. In line with a safety-focused approach, we recommend initiating cannabis when the patient is not performing safety sensitive activities until the absence of impairment has been established, as is done with many other pharmacotherapies.

2.1.3. Relative contraindications

Individuals under the age of 25 years. In patients under 25 years, careful consideration should be given to the risks versus benefits of cannabis use. Exposure to large THC doses and regular use has also been associated with risk of persistent cognitive effect, social dysfunction, anxiety, depression, and cannabis dependence in youth [19,25,63]. As such, there is an increased risk of cannabis use disorder in youth. In those at risk, younger age of initiation of cannabis has been associated with an earlier onset and worse outcomes of schizophrenia and bipolar disorder [33].

Cannabis use disorder (CUD). Cannabis, more specifically THC, is contraindicated in patients with an active or a history of cannabis use disorder. Recent literature has proposed CBD as a harm reduction tool in cannabis use disorder [73].

Substance use disorder or patients at risk for cannabis use disorder. Clinicians should screen for potential problematic use with risk assessment tools. If a patient has an active or history of substance use disorder or is at risk of CUD, careful consideration on cannabis risk should be done before initiation [43]. In these select patient populations more frequent monitoring and follow-up should be conducted (See *Follow up* section).

2.1.4. Contraindications

Unstable cardiovascular disease. THC can cause acute cardiovascular effects such as tachycardia, and postural hypotension [49]). There are no QTc interval issues identified with cannabis use [56]. Cannabis should not be used with unstable cardiac conditions including acute congestive heart failure, critical aortic stenosis, poorly controlled atrial fibrillation and coronary artery disease.

In those at risk for CVD or with stable CVD, clinicians should monitor frequently. Smoking cannabis should be avoided in all patients, and in particular, this population. If cannabis is deemed appropriate for use, CBD dominant products are recommended. If symptoms are not adequately controlled with CBD, clinicians could consider the slow addition and titration of THC with frequent monitoring.

Respiratory disease. Smoking cannabis releases harmful chemicals, such as carbon monoxide, polyaromatic hydrocarbons, ammonia and carcinogens, through combustion [35,48,50,61] . There is substantial evidence associating cannabis smoking and worsening respiratory symptoms (e.g. cough, sputum production, wheeze, chest tightness) as well as more frequent chronic bronchitis episodes [34,49].

Currently, it is unclear if cannabis use is associated with the development of specific respiratory illnesses such as COPD or asthma [49]. No overall association has been found between cannabis smoking and lung cancer [29,65]. In general, but particularly for those with respiratory disease, smoking cannabis is not recommended. Cannabis oral forms are safest within this patient population.

Psychosis and bipolar disorder. Daily THC use may worsen symptoms in individuals with bipolar disorder and/or current psychosis [11,31]. In certain individuals, such as those with genetic predispositions, the use of THC may induce psychosis. These genetic factors were estimated to explain 69-84% of the link between cannabis and psychosis [36]. Other risk factors include early life stressors, early age of cannabis initiation and regular use, and the use of high THC-containing products [27,57]. Extra caution should be taken when patients have a personal or family history of these conditions.

Pregnancy and breastfeeding. Cannabis is contraindicated in pregnancy due to the risk of neonatal morbidity [6,18,30,46,58]. First trimester use is associated with negative pregnancy outcomes [6]. Concurrent cannabis and tobacco smoking increases the risk of adverse perinatal outcomes [18]. Increased risk of major malformation is not supported by current evidence [9,46]. Though evidence is limited, there continues to be a concern for the effect of cannabis on neurodevelopment. For breastfeeding mothers, cannabinoids are detectable in breast milk for up to 6 days [3].

2.2. Screen for drug interactions (Step 2)

Generally, it is believed cannabis can be safely used with the majority of medications [54,59]. A common concern is the concomitant use with CNS depressants leading to potential pharmacodynamic interactions. While importantly there are few formal drug-drug interactions, additive pharmacodynamic effects could lead to sedative or cognitively impairing adverse events. Clinicians should screen for recreational, prescription, and over-the-counter medications. Common depressants such as alcohol, opioids, antipsychotics, benzodiazepines, tricyclic antidepressants, or antiepileptics may worsen sedation & cognitive impairment when coingested with cannabis [29,41].

Cannabis is metabolized in the liver by CYP 450 isoenzymes. THC is

predominantly oxidized by CYP2C9, CYP2C19, and CYP3A4. CBD is predominantly metabolized by CYP2C19 and CYP3A4. As such, CYP inhibitors or inducers may alter serum levels of these cannabinoids via pharmacokinetic drug interactions. Notably, CBD is a potent CYP 3A4 inhibitor and risks interacting with some medications in the following table ([3,4,21] Currently known cannabinoid drug interactions are summarized in Table 2.

It should be noted that although cannabis could theoretically impact drugs metabolized by the CYP enzyme family, in many cases, the relevance of cell or animal experimental findings has not yet been established in humans [3]. Clinical trials involving Nabiximols have the most robust data surrounding clinical drug interactions and found most to be not clinically significant. Instead, pharmacodynamic interactions are more common with compounded sedation being seen with a number of drugs. However, more safety and drug interaction studies are needed. If a patient is at high risk, using high doses of cannabinoids, or is using a medication with a known or potential drug interaction careful monitoring should be implemented (See *Follow up* section).

How do I proceed if there is potential for a drug interaction?.

If a potential drug interaction is found, clinicians should carefully consider if both therapies are needed. If cannabis benefit is still deemed to outweigh risk, increased monitoring for potential adverse events and/or drug levels is recommended. Approaches for managing drug interactions include initiating at a low dose, tapering medications if appropriate, decreasing THC or CBD dose depending on the interaction, switching chemovars, or discontinuing cannabis use.

2.3. Safety considerations for initial route of administration (Step 3)

Each route of administration has different pharmacokinetic properties, and thus different onset and duration of action (see Appendix 1, Table B). The two most common medical cannabis routes of administration are inhalation and oral (Table 3). Oral oil is preferred in most patients as it eliminates respiratory risk and allows for accurate dosing. Inhalation can be used, however, there is an increased risk for respiratory harm, especially in those with pre-existing respiratory conditions. If inhalation is deemed necessary, dried cannabis vaporization is recommended. Concentrates should be avoided due to the potential for contaminants, difficulties in accurate dosing, and the potential for health harms such as EVALI. Other dosage forms are available (eg sprays, suppositories, topicals, and edibles) but there is insufficient safety evidence to make recommendations at this time.

Regulatory protocols within a region and the source patients are obtaining their cannabis from dictates the risk of exposure to product contaminants. For example, in the legal Canadian market, cannabis producers must pass strict federal government mandated regulations with standardized testing for contaminants. In unregulated markets, there is a much greater risk that products may contain harmful matter. Extraction processes to form concentrated cannabis products (eg. 'dabs' or shatter) can involve solvents, which may leave toxic residues for consumption. Certain chemicals used in THC-containing e-cigarette or vaping products are also of particular concern (see EVALI section for more details). High-quality cannabis products, free of contaminants and toxins, and from a regulated source, which has been tested according to regulatory requirements, are preferred for all patients ([43], chapter 31). Clinicians in collaboration with their patients should consider product safety risks of concentrated products if they are being used in treatment (see Appendix 1, Table A).

2.4. Safety considerations for chemovar (strain) (Step 4)

THC is the primary psychoactive component of cannabis. The majority of adverse events related to cannabis are THC-dose dependent. By contrast, CBD has a greatly reduced adverse event profile of cannabis use. Patient circumstance should be carefully considered when choosing an appropriate strain, as each strain could lead to a difference in response (Table 3). In particular, there is a safety risk of high THC products in specific groups (see Table 1) such as the elderly, under 25, history of mental health, heart conditions, other conditions where there may be sensitivities with THC (e.g. fibromyalgia) with symptoms that may compound the effects of THC, and those in safety sensitive occupations ([24,45].

Due to drug interactions, there is a safety risk with CBD products in some patients (e.g. taking clobazam or calcineurin inhibitors). The utility of CBD-dominant products may improve safe cannabis initiation as it is considered non-impairing. There is limited evidence that CBD may counter adverse events related to THC, although commonly done by some clinicians in practice. It is important to note that many CBD dominant products will contain some THC. For example, if a patient is taking 50 mg of a 50:2 CBD dominant product, they will still receive a 2 mg dose of THC. This may be a consideration when increasing doses, particularly in patients sensitive to THC. However, with a slow titration approach most patients will develop tolerance to the relatively small dose of THC.

2.5. Initiate with low-dose, slow titration strategy (Step 5)

Once chemovar and route of administration have been selected, patients should be initiated with a low-dose, slow titration regimen (Table 4). To reduce risk of impairment or adverse events, clinicians may consider dosing based on the mg of THC, not percent concentration. A slow dose titration can help to build tolerance to THC and reduce the risk of adverse events and impairment. To optimize safety, the goal is to reach the lowest dose that offers symptom control with minimal or no adverse events. From a safety standpoint, consider a CBD dominant product first for daytime use. This is especially important in medically vulnerable populations. Using an oral oil is ideal as it allows for more flexible and accurate dosing. If THC is needed, start at a low dose at bedtime, and slowly titrate up. If daytime THC is needed, it should be added slowly to the initial CBD-dominant treatment regime until goals of therapy are achieved. At time of cannabis initiation, we recommend keeping all concomitant medications doses stable, unless it is known to interact and monitoring warrants adjustment.

2.6. Set monitoring frequency (Step 6)

Following initiation, monitoring is an essential component to ensuring safety. The monitoring frequency depends on prior cannabis experience, comorbid medical conditions, and the patient's ability to adhere to the treatment plan (see Appendix 1, Table C). Generally, the initial follow up is set within 1-3 months of starting medical cannabis. Special populations often need more frequent follow up. If the patient has any of the conditions listed in Table 1, consider initial follow-up every 2-3 weeks until the patient is on a stable dose. If a patient has minimal experience, moderate to severe comorbidities, or difficulty adhering to the treatment plan consider initial follow up within 1 month of initiation. If the patient is an experienced user, has minimal comorbidities, and is able to adhere to the treatment plan following up within 3 months of initiation is usually appropriate. Clinicians should adjust recommendations based on their experience and the patient's condition. Cost of medical care may influence a patient's monitoring schedule. CRCs should be aware of the guidelines set out by their regulatory body.

3. Follow up

Following initiation, monitoring and management of adverse events and potential drug interactions are the primary focus of ensuring patient safety. Clinicians should address the fundamental components of efficacy and symptom control, assessment and management of adverse events, and drug interactions (Fig. 2). It is recommended to encourage

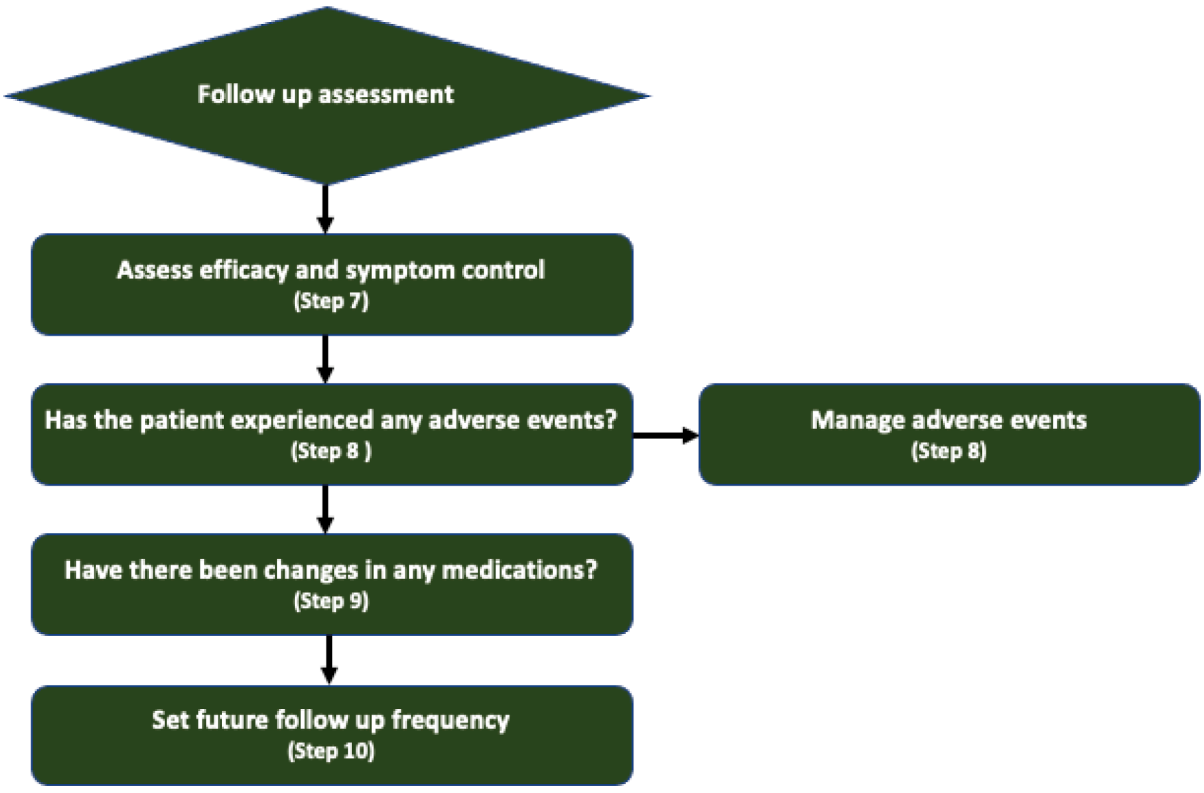

Fig. 2. Key considerations for follow up assessments for medical cannabis.

patients to track their cannabis use, including products used, route of administration, dose, adverse events, and changes in symptoms post dose.

3.1. Assess efficacy and symptom control (Step 7)

An important component of assessing the risk vs benefit for the patient is a symptom response assessment with cannabis use. In addition to product details (chemovar, route, dose), improvements or worsening of symptoms should be tracked (dosing logs available at Safe-cannabis.com in the dosing section). We recommend clinicians assess symptom control through objective, validated tools (e.g. GAD-7, PHQ-9, BPI), where appropriate. These can be useful tools to track outcomes and help inform future dosing or direction of treatment.

3.2. Has the patient experienced any adverse events? (Step 8)

Adverse events are most often THC-dose dependent and dissipate over time through tolerance [22,44]. Many can be prevented, or at least mitigated, with low dose initiation and slow titration. Common adverse events include drowsiness/fatigue, dizziness, dry mouth, nausea, effects on cognitive function and deficits in motor function (see Appendix 1, Table D) [29,44]. These are similar across diverse patient groups [29], and should be assessed at each follow-up visit. Adverse event management approach is determined by the severity (see Appendix 1, Table E). Clinicians should engage the patient in a discussion on the potential impact of the adverse events. Many of these events can be managed with adjustments to administration factors such as chemovar, dose, and route of administration.

3.3. Have there been changes in any medications? (Step 9)

It is important for patients taking cannabis to be regularly assessed for changes in their other pharmacotherapy. This could impact cannabis dosing and the potential for drug interactions. If the patient has initiated new therapy, clinicians are strongly encouraged to evaluate these changes for potential drug interactions. Refer to *Potential Drug Interactions* for cannabinoid related drug interactions and management approaches.

3.4. Set future follow up frequency (Step 10)

Future follow up frequency depends on the individual's personal and medical history (See Table 1 and step 6). In addition to the CRC's experience. Once a patient is on a stable cannabis dose, consider follow up visits every 3-6 months or as per clinical circumstance. More frequent follow up is recommended if the risk benefit ratio changes for the patient e.g. new medication or diagnosis. Clinicians should be diligent in assessing the above components at each follow-up to ensure patient safety. All future follow-ups should be based on the patient's needs and clinician's experience.

4. Conclusion

A safety focused approach at each step of a patient's cannabis journey is necessary. Prior to initiation, clinicians should screen for precautions and contraindications as well as potential drug interactions. It is important to know if a patient belongs to a specific group at increased risk with cannabis use. The safest chemovar, route of administration and starting dose, specific to the patient, should be considered. When initiating cannabis, a low dose, and slow titration method should be used. Following initiation, monitoring for adverse events and drug interactions is crucial. Adjustments to treatment plans should be made to mitigate any issues or potential risks that arise. Tools have been developed to aid CRCs in improving cannabis safety. These tools are available at Safe-cannabis.com.

Just as more research must be completed on the efficacy of medical cannabis, it is equally important to assess safety to reduce the risks of use. There is a great need for more robust efforts in assessing safety factors regarding medical cannabis use with a wide range of conditions.

Declaration of Competing Interest

Author CM is the Medical Director of Greenleaf Medical Clinic and Chief Medical Officer for Translational Life Sciences. She is on the Board of Directors for the Green Organic Dutchman. She is an advisor to Andira, Active Patch Technologies and Dosist. She previously advised Emerald Health Therapeutics and Strainprint. She has attended advisory board meetings for Syqe Medical, and Shoppers Drug Mart. Additionally, she has provided medical consultation and/or received support for industry sponsored continuing medical education from: Aleafia, Spectrum, Tilray, Numinus, Aurora & MD Briefcase.

Author LL has no conflicts of interest

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Supplementary materials

Supplementary material on cannabis concentrates, pharmacokinetic properties, monitoring frequency, management of adverse events can be found, in the online version, at doi:10.1016/j.ejim.2021.05.002.

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