Clinical management of cannabis withdrawal

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Abstract

Background and Aims: Cannabis withdrawal is a well-characterized phenomenon that occurs in approximately half of regular and dependent cannabis users after abrupt cessation or significant reductions in cannabis products that contain Δ^9-tetrahydrocannabinol (THC). This review describes the diagnosis, prevalence, course and management of cannabis withdrawal and highlights opportunities for future clinical research.

Methods: Narrative review of literature.

Results: Symptom onset typically occurs 24–48 hours after cessation and most symptoms generally peak at days 2–6, with some symptoms lasting up to 3 weeks or more in heavy cannabis users. The most common features of cannabis withdrawal are anxiety, irritability, anger or aggression, disturbed sleep/dreaming, depressed mood and loss of appetite. Less common physical symptoms include chills, headaches, physical tension, sweating and stomach pain. Despite limited empirical evidence, supportive counselling and psychoeducation are the first-line approaches in the management of cannabis withdrawal. There are no medications currently approved specifically for medically assisted withdrawal (MAW). Medications have been used to manage short-term symptoms (e.g. anxiety, sleep, nausea). A number of promising pharmacological agents have been examined in controlled trials, but these have been underpowered and positive findings not reliably replicated. Some (e.g. cannabis agonists) are used 'off-label' in clinical practice. Inpatient admission for MAW may be clinically indicated for patients who have significant comorbid mental health disorders and polysubstance use to avoid severe complications.

Conclusions: The clinical significance of cannabis withdrawal is that its symptoms may precipitate relapse to cannabis use. Complicated withdrawal may occur in people with concurrent mental health and polysubstance use.

KEYWORDS
assessment, cannabis withdrawal syndrome, clinical management, pharmacology, prevalence, time course

DEPENDENCE, WITHDRAWAL STATES AND CLINICAL MANAGEMENT

Description

Cannabis withdrawal refers to symptoms that occur after abrupt cessation or significant reductions in the use of cannabis products containing Δ^9-tetrahydrocannabinol (THC), the main psychoactive component in cannabis. These symptoms occur most often in regular and heavy cannabis users and the most common symptoms are anxiety, irritability, anger or aggression, disturbed sleep/dreaming, depressed mood and loss of appetite. Less commonly reported physical symptoms include chills, headaches, physical tension, sweating and stomach pain [1, 2]. Cessation of short-term cannabidiol (CBD), a non-psychoactive cannabinoid, does not appear to result in withdrawal [3].

Symptom onset typically occurs 24–48 hours after cessation and most symptoms generally peak at days 2–6. The duration and severity of cannabis withdrawal is associated with the amount of cannabis consumed before cessation, but can vary considerably. In heavy users withdrawal symptoms can occur for up to 2–3 weeks or longer.

Prevalence

A meta-analysis pooling studies of more than 20 000 regular and dependent cannabis users estimated that 47% of individuals reported cannabis withdrawal measured by standardized scales [4]. The prevalence in community samples was 17%, increasing to 54% in outpatient samples and 87% in inpatients [4].

The prevalence of cannabis withdrawal symptoms is higher in users with a history of daily cannabis use, concurrent cannabis and tobacco use and other substance use disorders [4].

Objectives of management

Cannabis withdrawal does not carry a high risk of severe adverse outcomes. The presence of medical or psychiatric comorbidities such as polysubstance use and dependence may result in more severe complications and symptoms of cannabis withdrawal, necessitating additional management. The clinical significance of cannabis withdrawal is that it may undermine abstinence by precipitating a relapse to cannabis use which immediately relieves these symptoms [5]. Irritability and mood effects can also negatively impact personal relationships and work productivity.

Synthetic cannabinoids (SCBs) are classed as new psychoactive substances (NPS) and are made in clandestine laboratories. Unlike cannabis, SCBs are a heterogeneous group that may contain multiple, typically synthetic compounds with broad structural diversity and are therefore not reviewed in this paper. SCBs can be 2–100 times more potent than THC [6], are more likely to result in problematic use and faster development of tolerance and potentially result in more severe withdrawal than natural cannabis [7]. Their mechanisms and effects remain poorly understood.

Cannabis dependence

Individuals with cannabis use disorder (CUD) generally experience greater severity and duration of cannabis withdrawal symptoms than those without CUD. This is most probably related to the greater frequency and quantity of their cannabis use and their heavier exposure to THC [8]. CUD is characterized by persistent cannabis use despite negative effects on the social functioning and physical or mental health of the user or the health of other individuals. Two diagnostic systems classify and define the severity of the disorder: the Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 [1] and International Classification of Diseases (ICD)-11 [9]. CUD severity is coded in DSM-5 as mild (presence of two to three symptoms), moderate (presence of four to five symptoms) or severe (presence of six or more symptoms). ICD-11 classifies cannabis use into hazardous cannabis use (potential to cause harm), harmful pattern of cannabis use (causing harm) and cannabis dependence.

Neurobiological evidence

The cannabis plant contains approximately 120 cannabinoids, the most studied of which are THC and CBD. The body's own endogenous cannabinoids act as partial agonists of the body's CB1 and CB2 receptors [10, 11], as does THC [12], whereas CBD acts as an allosteric modulator of these receptors [13, 14]. The psychoactive effects of THC are underpinned by its strong affinity for CB1 receptors, which are predominantly distributed within the brain. CB1 antagonists, such as rimonabant, reduce the subjective effects of cannabis, demonstrating the role of CB1 binding in the psychoactive effects of cannabis use [15]. THC has a much lower affinity for the CB2 receptor that is predominantly found in immune cells. Conversely, CBD has a stronger affinity for the CB2 receptor, but has a relatively much lower affinity for either receptor than THC.

There are endogenous cannabinoid neurotransmitters in humans and other animals. The best-characterized are anandamide (AEA) and 2-arachidonoylglycerol (2-AG). These endocannabinoids are degraded by enzymes that include fatty acid amide hydrolase (FAAH) for anandamine and monoacylglycerol lipase (MAGL) for 2-AG. THC is metabolized by the enzymes CYP3A4 and CYP2C9 [16]. FAAH binding is reduced in chronic and recent cannabis users [17], and inhibition of FAAH using PF-04457845 has been shown to reduce cannabis withdrawal [18].

There is good neurobiological and clinical evidence for a pharmacologically specific cannabis withdrawal syndrome. CB1 antagonists precipitate specific withdrawal symptoms in animal models of cannabis dependence [19]. In human studies, administration of CB1 agonists (THC) blocks or relieves withdrawal symptoms [20–22]. Neurobiological and clinical studies indicate that symptoms of cannabis withdrawal

are consistent with the core symptoms of other substance withdrawal syndromes and reflect neurochemical changes in the limbic system [2].

Cannabis withdrawal criteria DSM-5 and ICD-11

Withdrawal was included as a distinct disorder and as a CUD diagnostic criterion item in DSM-5. Cannabis withdrawal is also included in ICD-11 (Table 1).

Withdrawal severity

In most instances, cannabis withdrawal is not severe and does not have a high risk of severe adverse outcomes. Medical or psychiatric comorbidities increase the risk of severity and the requirement for additional management. Cannabis withdrawal severity can be evaluated by a clinical examination of the number and intensity of DSM-5 or ICD-11 cannabis withdrawal features and by administering standardized measures of cannabis withdrawal. Unlike symptoms of other substance use disorders (SUDs), DSM-5 and ICD-11 assess only the presence or absence of cannabis withdrawal symptoms, rather than their severity. The most clinically relevant criterion is the degree of patient distress or impairment in functioning. This can be assessed both subjectively (e.g. anxiety, sleep quality) and objectively (e.g. weight loss, fever).

The two most widely used cannabis withdrawal scales are the 16-item marijuana withdrawal checklist (MWC [23]), a revised version of the original 22-item scale [24], and the 19-item cannabis withdrawal scale (CWS [25]; see Supporting information). Both the MWC and CWS were developed before DSM-5. There is considerable overlap of features between DSM-5 and MWC and CWS, but not complete concordance. An adaption of the MWC, the 14-item composite withdrawal scale (WDS [26]), corresponds more closely with cannabis withdrawal symptoms described in the DSM-5. By comparison with other substance withdrawal scales (e.g. alcohol withdrawal scale), there has been limited psychometric validation of the various cannabis withdrawal scales.

Differential diagnosis

Because many cannabis withdrawal symptoms are not specific to cannabis, a differential diagnosis needs to determine if they are better explained by withdrawal from another substance (e.g. tobacco or alcohol) or are symptoms of a comorbid mental disorder or medical condition.

Polysubstance use

People with a CUD are more likely to use other substances. In nationally representative US surveys, people with a CUD in the past 12 months were six times more likely to have an alcohol use disorder and nine times more likely to have another drug use disorder [27]. Three in four cannabis users seeking treatment for a CUD will have another SUD [1]. Because of the high prevalence of comorbid substance use and dependence, it is important to know if the patient only wants to cease cannabis use, or some or all of the substances that they use. In outpatient settings the patient may prefer to continue to use other substances. There are insufficient studies to decide whether it is better to withdraw from multiple substances sequentially or concurrently. In an inpatient setting, all non-prescribed substances are usually stopped.

TABLE 1 Cannabis withdrawal criteria: DSM-5 and ICD-11

DSM-5 Cannabis withdrawal disorder (292.0) [1]	ICD-11 Cannabis withdrawal (6C41.4) [9]
Signs and symptoms	Description
Three (or more) of the following signs and symptoms develop after cessation of heavy and prolonged cannabis use (daily or almost daily use over a period of at least a few months):	...that occurs upon cessation or reduction of use of cannabis in individuals who have developed cannabis dependence or have used cannabis for a prolonged period or in large amounts
1. Irritability, anger or aggression 2. Nervousness or anxiety 3. Sleep difficulty (e.g. insomnia, disturbing dreams) 4. Decreased appetite or weight loss 5. Restlessness 6. Depressed mood 7. At least one of the following: physical symptoms causing significant discomfort: abdominal pain, shakiness/tremors, sweating, fever, chills or headache	Presenting features of cannabis withdrawal may include: irritability, anger or aggressive behaviour, shakiness, insomnia, restlessness, anxiety, depressed or dysphoric mood, decreased appetite and weight loss, headache, sweating or chills, abdominal cramps and muscle aches
The signs or symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning The signs or symptoms do not relate to another medical condition or better explained by another mental disorder, including intoxication or withdrawal from another substance	Is a clinically significant cluster of symptoms, behaviours and/or physiological features, varying in degree of severity and duration

Withdrawal from other substances (whether prescribed or recreational) can produce similar symptoms to cannabis withdrawal. For example, opiate and alcohol withdrawal can produce irritability, anger or aggressive behaviour, shakiness, insomnia, restlessness, anxiety, depressed or dysphoric mood, decreased appetite and weight loss, headache, sweating or chills, abdominal cramps and muscle aches. In the case of alcohol withdrawal delirium tremens, this is a medical emergency. A key tool in a differential diagnosis is the cessation of cannabis use with 24–48 hours of onset and an improvement in symptoms after 4–7 days of abstinence, with careful assessment of other substance use and abstinence patterns.

We know little about interactions between the effects of cannabis and other drugs [28], but polysubstance use may increase the severity of withdrawal. Cannabinoid receptors are major targets, directly or indirectly, for many drugs of abuse including prescription analgesics, but interactions between these drugs are poorly understood. Additive intoxication and withdrawal effects may occur when cannabis is combined with central nervous system (CNS) depressants such as alcohol and opioids (e.g. drowsiness, ataxia) and some benzodiazepines or new psychoactive substances (NPS) [29]. Patients who co-use tobacco and cannabis report more withdrawal symptoms than those who use cannabis without tobacco [30]. A clinical priority should be to identify which substances have been used and to manage the withdrawal symptoms of the highest-risk substances or substance combinations.

Psychiatric comorbidity

There is a well-documented dose–response relationship between the level of cannabis use, CUD and psychiatric comorbidity. A differential diagnosis therefore requires assessment of concurrent mental health disorders, symptoms of which may be exacerbated by or mimic cannabis withdrawal. In a national stratified Australian sample, 70% of adults who met CUD criteria in the past year had at least one other psychiatric disorder [31]. In US national surveys, having a CUD in the past 12 months is associated with increased risk of post-traumatic stress disorder [PTSD; odds ratio (OR) = 4.3], personality disorder (OR = 4.8), mood disorders (OR = 3.8) and anxiety disorders (OR = 2.8) [27]. Heavy cannabis use increases psychosis risk, and cannabis use worsens symptoms of schizophrenia [32].

Physical comorbidities

It is beyond the scope of this review to provide a comprehensive description of physical conditions that should be considered in a differential diagnosis for cannabis withdrawal. As cannabis withdrawal symptoms can mirror other physical disorders, a comprehensive medical review with an emphasis on gastrointestinal and neurological systems is recommended.

GOLD-STANDARD CURRENT PRACTICE

Setting and rationale for inpatient/outpatient

Inpatient admission is rarely required for uncomplicated medically assisted withdrawal (MAW). Supervised or inpatient treatment for withdrawal should be considered if the patient is a polysubstance user and has a history of complicated withdrawal from these other substances. If exacerbation of a mental health condition is likely to produce major functional impairment, or increase the risk of self-harm, supervised inpatient MAW should also be considered. Medical oversight is recommended for patients with medical conditions that may be adversely affected by substance withdrawal. Individuals who have been unable to manage their cannabis use in an outpatient setting should be considered for inpatient support.

Time-frame

The onset of cannabis withdrawal symptoms typically occurs 24–48 hours after cessation of use. The early phase of withdrawal is usually characterized by insomnia, irritability, decreased appetite, shakiness and, less often, sweating and chills. These early symptoms are most likely to peak at days 2–6. They improve as THC levels reduce over 7 days of abstinence. Anger and aggression and depressed mood may occur as early as 1 week into cannabis withdrawal but typically peak after 2 weeks of abstinence [33, 34] (Figure 1). Sleep disturbances may continue for several weeks or longer.

THC-COOH is generally associated with severity of the cannabis withdrawal syndrome, as measured by scores on the MWC [8]. Future research studies may determine if THC-COOH levels can more precisely guide the management and duration of cannabis withdrawal [8]. Figure 1 displays typical reductions in mean daily creatinine-normalized THC-COOH levels after abstinence in heavy, chronic cannabis users [35].

There is a large amount of variation in the course and severity of cannabis withdrawal. Some patients who report low levels of cannabis use and few CUD symptoms (e.g. only two to three DSM-5 criteria) report uncomfortable withdrawal symptoms that significantly impair their day-to-day functioning. There are limited empirical data on the degree to which individual differences in physical, psychiatric or metabolic factors contribute to cannabis withdrawal severity. Up to 50% of between-individual differences in cannabis withdrawal can be attributed to genetic variation [36]. Some studies of recreational and regular cannabis users [37] and those seeking treatment [26, 38] report that females may experience more severe cannabis withdrawal symptoms than males, even when matched for cannabis use and other demographic characteristics.

Need for pre-detoxification harm reduction

Cannabis pre-detoxification harm reduction strategies are not well studied and there is no standard practice. As with other substances,
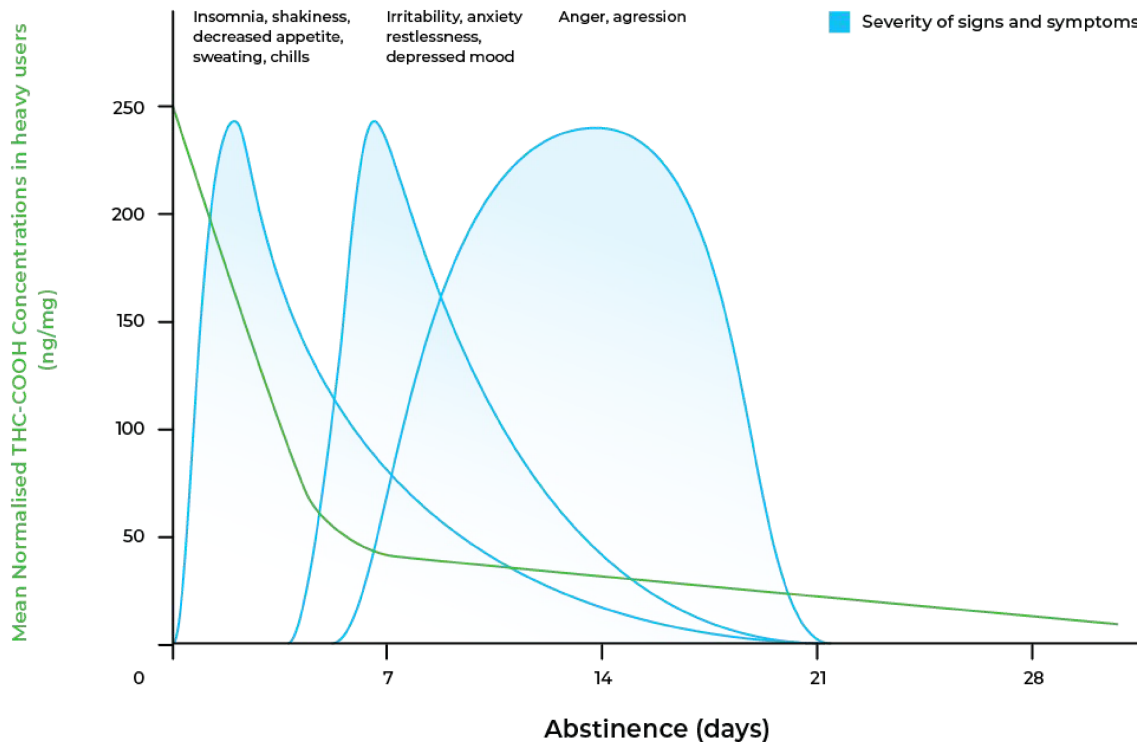
FIGURE 1 Typical course of cannabis withdrawal. Adapted from Goodwin *et al.* [35] and Queensland Health (2012) [34, 90]. Typical urinary tetrahydrocannabinol carboxylic acid (THC-COOH; the main secondary metabolite of THC) levels are drawn from Goodwin *et al.* [35] and reflect high-range, chronic cannabis use

an incremental and slow reduction in cannabis intake and/or use of lower THC products over an extended period (weeks) may reduce the probability and severity of withdrawal symptoms.

Risks/benefits

There are few risks related directly to cannabis withdrawal. The greatest risk is relapse [5]. Previously highlighted in this review is elevated risk of polysubstance use and concurrent withdrawal from higher-risk substances. If cannabis withdrawal exacerbates depression ($\pm$ suicide), anxiety and psychosis, then risks are increased and more regular monitoring and delay in detoxification may be clinically indicated. All medications carry risk of side-effects. Consideration should be given to the potential side-effects of using pharmacotherapies that are largely untested in this population, compared to the temporary uncomfortable withdrawal period.

Non-pharmacological interventions

To our knowledge, there are no high-quality studies on the most effective behavioural approaches and no studies that compare the effectiveness of behavioural and pharmacological approaches to

managing withdrawal. Most pharmacological studies of withdrawal include some form of concurrent behavioural intervention, but the differential efficacy of these behavioural approaches has not been assessed (Table 2).

A 12-week single-arm cognitive behavioural therapy (CBT) study randomly assigned 13 regular cannabis users to selective serotonin re-uptake inhibitors (SSRI) or placebo. It found no significant differences on the Clinical Institute Withdrawal Assessment (CIWA) scores (adapted for cannabis) [39] between patients who relapsed and those who did not. Changes in CIWA scores in response to CBT were not reported nor any differences between those given SSRI or placebo [40].

Despite limited evidence, standard clinical practice typically includes psychoeducation on the course and symptoms of withdrawal, coping with craving exercises, nutrition, hydration, physical exercise and sleep hygiene. It can also include motivational approaches and coping skills training [41]. Skills training in CBT such as relaxation approaches, pleasant activity scheduling, managing stress/mood/anger and goal-setting may be of clinical benefit.

Physical exercise has been associated with improved scores in the Marijuana Craving Questionnaire—short form (MCQ-SF) in a pilot study (n = 10) of non-treatment-seeking, cannabis-dependent adults [42]. Standard sleep hygiene protocols [43] and CBT-insomnia (CBT-I [44]) may improve sleep in cannabis withdrawal, but this has not been well studied [45].

TABLE 2 Pharmacotherapy studies for cannabis withdrawal

Medication	Approved for use in cannabis withdrawal	Primary or Secondary outcome in study	Design and main findings	Limitation and future research
Cannabis agonists				
Dronabinol	No	Secondary [46, 54]	Randomized, double-blind 12 week outpatient study of cannabis-dependent users [46]. Primary outcome was cannabis abstinence. Patients (n = 79) were titrated to 20 mg twice daily over the period of 1 week, or placebo (n = 77). Both groups received weekly coping skills intervention and MET Dronabinol increased treatment retention and reduced cannabis withdrawal symptoms (measured by the WDS) over time compared to placebo. Medication was well tolerated and no difference in side effects reported between groups [46] An RCT by the same authors as [46] found no benefit from adding lofexidine (a potent α_2-adrenergic receptor agonist with moderate agonist effects) to dronabinol (n = 61) on cannabis withdrawal (measured by the WDS), compared to placebo (n = 61) in cannabis-dependent individuals [54]	Replication RCTs required with cannabis withdrawal as a primary outcome. Greater than one-third attrition among studies Outcomes relied on self-report. Not possible to examine dronabinol in absence of lofexidine
Nabiximols, Nabilone	No	Primary [48]	Randomized, double-blind inpatient study of cannabis-dependent users (mean 22.98 g/week) [48]. Patients (n = 27) completed a 6-day regimen of nabiximols providing a maximal daily dose of 86.4 mg THC and 80 mg CBD or placebo (n = 24). Both groups received CBT-based self-completed work-books during a 9-day admission Nabiximols reduced CWS scores for the duration of treatment and improved retention relative to placebo. No serious adverse events or differences in side effects reported between groups [48]	Larger-scale validation RCTs required to assess the effectiveness of nabiximols in cannabis withdrawal, including dose–response data. Treatment withdrawal high (> 1/3). Baseline CWS score differed between groups
		Secondary [56]	Cannabis-dependent outpatients were randomized (double-blind) to either as-needed (self-titrated) nabiximols spray (n = 20) up to 113.4 mg THC/105 mg CBD or placebo (n = 20) daily for 12 weeks. Primary outcomes were tolerability and cannabis abstinence. Secondary outcomes were cannabis use,	Pilot study with small sample size. High variability in amount of nabiximols self-administered

(Continues)

TABLE 2 (Continued)

Medication	Approved for use in cannabis withdrawal	Primary or Secondary outcome in study	Design and main findings	Limitation and future research
			withdrawal and craving. Both groups received MET + CBT	
			No difference between nabiximols and placebo in withdrawal scores (MWC). Over the 12-week study, reduction in cannabis craving (MCQ-SF) statistically favoured nabiximols. No serious adverse events or differences in side effects reported between groups [56]	
		Primary [49]	Cannabis-dependent participants (n = 16) completed an 8-week double-blind trial consisting of four smoke-as-usual conditions and four cannabis abstinence conditions during which they administered self-titrated and high dose Sativex nasal spray, and self-titrated and frequent dose placebo spray. Primary outcomes were medication tolerability, serious adverse events, craving and withdrawal	Small sample size and short duration Sativex contains approximately 1:1 ratio of THC: CBD, potentially obscuring the respective contribution of CBD and THC
			High fixed doses of Sativex were well tolerated and significantly reduced withdrawal (CWS and MWC) during abstinence relative to placebo. Cravings (MCQ) were not reduced. Self-titrated Sativex doses were lower than fixed doses, but self-titrated dosing also showed limited efficacy compared to placebo	
	No	Secondary [62]	Cannabis-dependent outpatients were randomized to either 2 mg/day of nabilone (n = 10), maximum dose reached after a 3-week escalation or placebo (n = 8) for 10 weeks [62]. Primary outcomes were safety and tolerability. Cannabis craving and anxiety were secondary outcomes. Both groups received behavioural 'medication management'	Pilot study of small sample size and short duration
			No difference between nabilone and placebo on cannabis craving (MCQ) or anxiety (BAI). No serious adverse events or differences in side effects reported between groups [62]	
Nabilone and varenicline	No	Secondary [60]	Non-treatment-seeking tobacco and cannabis co-users smoking at least two joints a day for at least 6 days a week were randomized to receive varenicline (n = 28) or a placebo (n = 18) in a double-blind placebo-controlled trial that consisted of an outpatient phase	Assessment of cannabis withdrawal symptoms did not use standardized scales. Low, unbalanced sample size between study arms

(Continues)

TABLE 2 (Continued)

Medication	Approved for use in cannabis withdrawal	Primary or Secondary outcome in study	Design and main findings	Limitation and future research
			followed by an inpatient phase. During the inpatient phase all participants received nabilone and a placebo	
			The purpose of the outpatient phase was for varenicline titration and to discontinue tobacco smoking. Participants were not instructed to discontinue cannabis. In the inpatient phase participants received 4 mg twice daily nabilone and a placebo crossed-over across two 8-day medication phases. In this phase participants used experimental cannabis (days 1–2), followed by abstinence (days 3–5), and a 'relapse' period during which participants could purchase active cannabis (days 6–8). This order—cannabis consumption, abstinence and relapse—was repeated administering the countervailing medication (nabilone or placebo)	
			Outcomes during the outpatient phase were tobacco and other drug use and adverse events. During the inpatient phase outcomes included mood and craving measured using a VAS, sleep assessed using a wrist-worn monitoring system and VAS, and relapse defined as the number of inhalations that participants purchased during the relapse phase	
			The inclusion of nabilone significantly attenuated the withdrawal-related mood and sleep symptoms, except for VAS ratings of the term 'anxious'. Cannabis craving did not differ. Sleep onset was significantly increased and duration decreased during abstinence in participants receiving placebo in lieu of nabilone	
Oral THC	No	Primary [51]	Outpatients (n = 8) who used cannabis at least 25 days per month in the preceding 6 months completed a repeated-measures laboratory study consisting of three smoking-as-usual conditions (A), followed by an abstinence period (B, C and D) in a ABACAD design. During the abstinence periods participants were double-blind administered placebo, and a	Small sample size. It is possible that participants continued undetected low levels of cannabis use during abstinence

TABLE 2 (Continued)

Medication	Approved for use in cannabis withdrawal	Primary or Secondary outcome in study	Design and main findings	Limitation and future research
			low (30 mg) or high (90 mg) dose of oral THC. The low THC condition always preceded the high condition for safety reasons	
			The main outcome was withdrawal (MWC). A composite WDS was calculated from items within the MWC. Secondary outcomes consisted of cravings (MCQ), other symptomatology measured using the Brief Symptom Inventory, mood assessed using the POMS, heart rate and blood pressure	
			Compared to smoking-as-usual, administration of placebo resulted in significantly increased WDS and endorsement of five items on the MWC (aggression, craving, depressed mood, irritability and sleep difficulty). The effects of THC administration were examined in these items only. Administration of the low dose of THC significantly suppressed WDS, and responding on the irritability, aggression and sleep difficulty items. The high THC dose additionally suppressed endorsement of the depressed mood and craving items	
FAAH inhibitors				
PF-04457845	No	Primary [18]	Randomized, double-blind study of cannabis-dependent inpatients (5–8 days) then 3 weeks post-discharge [18]. Cannabis withdrawal was the primary outcome during hospital admission. Male patients (n = 46) were administered PF-04457845 4 mg once daily over the duration of the study or placebo (n = 24). No formal concurrent psychosocial treatment reported. PF-04457845 significantly reduced cannabis withdrawal (MWSC) in early stages (days 0–2) but not later stages (days 2–4) of inpatient treatment and resulted in less cannabis use post-discharge, compared to placebo. On average, the treatment group reported better overall sleep. There were no significant effects of interest on mood states measured using VAS. The drug group showed lower scores on a number of mood scales prior to drug administration (day 0). No serious adverse events were reported and no	Requires further studies with males and females for generalizability A large-scale multi-centre study is under way Group differences observed in withdrawal and mood ratings prior to drug administration (day 0)

(Continues)

TABLE 2 (Continued)

Medication	Approved for use in cannabis withdrawal	Primary or Secondary outcome in study	Design and main findings	Limitation and future research
			difference in side effects observed between groups [18]	
Atypical anti-convulsants				
Quetiapine	No	Secondary [47]	Randomized, double-blind placebo-controlled study of cannabis-dependent individuals seeking treatment. Randomly assigned to titrate to dose target (300 mg) or maximum tolerated quetiapine ($n = 66$) or placebo ($n = 64$). Primary outcomes were measures of daily cannabis use. Secondary outcomes were weekly urinary THC concentration, craving (MCQ; MCr), withdrawal (MWC), sleep problems (MOS-SS) and study retention. Quetiapine treatment significantly reduced cannabis withdrawal. With each week in the study, withdrawal scores decreased on average by 10.4% in the treatment and 6.5% in the placebo arm. No difference was observed in craving scores or sleep problems between the two groups. Time to dropout did not differ between groups	Large dropout, 44% of randomized participants withdrew prior to completion of the study
Anti-convulsants				
Gabapentin	No	Primary [50]	Randomized, double-blind study of treatment-seeking, cannabis-dependent outpatients [50]. Patients ($n = 25$) received gabapentin (1200 mg/day) for 11 weeks (followed by tapering) or placebo ($n = 25$). Manual-guided, abstinence-orientated individual counselling was provided to both groups. Gabapentin significantly reduced cannabis withdrawal (MWC) and cannabis use over the course of the study, compared with placebo. Mood (BDI-II) and sleep (PSQI) were also significantly improved. Medication was well tolerated and no difference in side effects reported between groups [50]	One-third of patients completed the trial. Validation studies with larger sizes and higher retention are required
Topiramate	No	Secondary [64]	Heavy adolescent and young adult cannabis users (80% met cannabis use or dependence criteria) were double-blind randomized to topiramate (titrated over 4 weeks then stabilized at 200 mg/day for 2 weeks, $n = 40$) or placebo	Approximately half (59%) of patients completed the trial. Topiramate was poorly tolerated by this young patient sample. Further research should first consider safety, dose and tolerability studies across age groups

(Continues)

TABLE 2 (Continued)

Medication	Approved for use in cannabis withdrawal	Primary or Secondary outcome in study	Design and main findings	Limitation and future research
			(n = 26) over 6 weeks. Both groups received MET. Primary outcomes were efficacy and feasibility in reducing cannabis use. Secondary outcome was depression scores (BDI), a symptom of cannabis withdrawal	
			There were no group differences on depression scores. Topiramate was poorly tolerated by this young sample (15–25 years of age) and of those participants who withdrew from the topiramate condition, 67% attributed their withdrawal to adverse medication side effects (depression, anxiety, difficulty with coordination or balance, weight loss and paraesthesia) [64]	
Mood stabilizers				
Lithium	No	Primary [53]	Randomized, double-blind study of treatment-seeking, cannabis-dependent inpatients received either oral lithium (500 mg, n = 19) or placebo (n = 22) twice daily for 8 days. Cannabis withdrawal (CWS) was a primary outcome. No concurrent formal behavioural treatment. 'Standard withdrawal care' reported	As noted by authors, two-thirds of study participants were administered nitrazepam (a benzodiazepine) for sleep problems during their inpatient stay. This may have impacted CWS scores. Attrition was high (50% in lithium group)
			Lithium did not significantly affect total CWS scores or treatment retention compared to placebo. No serious adverse events were reported and no difference in side effects observed between groups. Post-withdrawal measures of mood, anxiety and quality of life did not differ between groups [53]	
Divalproex	No	Primary [63]	Randomized, double-blind study of treatment-seeking, cannabis-dependent outpatients received either divalproex sodium (n = 13) or placebo (n = 12). Active medication was titrated to a maximum 2000 mg per day, starting at 500 mg daily for days 1–7, 1000 mg for days 8–13 and 1500 mg for weeks 2–6. Maximal dose was only provided to patients with blood levels < 50 ng/ml. Patients experiencing side effects or blood levels > 120 ng/ml had their dose lowered. Irritability, depression and anxiety (measured	Small trial. No standardized cannabis withdraw measure. > 90% male sample

(Continues)

TABLE 2 (Continued)

Medication	Approved for use in cannabis withdrawal	Primary or Secondary outcome in study	Design and main findings	Limitation and future research
			by SIS, HSC) were main outcomes and reflected some features of cannabis withdrawal. All patient received 'manualized relapse prevention therapy' There were no differences between groups on these selected withdrawal symptoms. Marijuana craving measured using a VAS reduced over the duration of the trial but did not differ between groups. There was no substantial increase in physical complaints among those individuals who initially received divalproex sodium compared to placebo. Three patients were withdrawn from divalproex for jitteriness, depression and/or abdominal cramping	
SSRI				
Escitalopram	No	Secondary [59]	Randomized, double-blind study of treatment-seeking, cannabis-dependent outpatients received either escitalopram (10 mg/day, n = 26) or placebo (n = 26) for 9 weeks (+ 14 weeks of follow-up). Cannabis withdrawal (CIWA) was a secondary outcome. Depression and anxiety (measured by BDI, STAI, HAQ) were also secondary outcomes and reflected some features of cannabis withdrawal. All patient received MET+CBT [55]. Escitalopram was no different to placebo on withdrawal scores or anxiety and depression scores during withdrawal and post-withdrawal periods. Most treatment attrition was from the escitalopram group (16 of 26). Adverse events and side-effects not specifically reported [59]	Small sample size. Half of patients completed the initial 9 weeks of the study
Bupropion	No	Secondary [52]	Randomized, double-blind study of treatment-seeking, cannabis-dependent outpatients received either nefazodone (n = 36) or bupropion-sustained release (n = 40) or placebo (n = 30) for 13 weeks (10 weeks medication). Nefazodone maximum dosage of 600 mg per day was reached beginning at 150 mg and increasing by 150 mg every 5 days if tolerated. Bupropion-sustained release	Approximately 50% of patients withdrew before completion of the 10-week medication phase

(Continues)

TABLE 2 (Continued)

Medication	Approved for use in cannabis withdrawal	Primary or Secondary outcome in study	Design and main findings	Limitation and future research
			started at 150 mg, after 3 days increasing to 300 mg per day, if tolerated. Cannabis withdrawal was a secondary outcome. Anxiety (HAM-A), irritability (SIS) and sleep disturbances (SMHSQ) reflected some features of cannabis withdrawal. All patient received a coping skills therapy programme	
			There were no significant differences in cannabis withdrawal symptoms between nefazodone or bupropion-sustained release, compared to placebo. Side effects were reported by 45% of the bupropion-sustained release group (mainly headaches and nausea) and 42% of the nefazodone group (mainly diarrhoea), compared to 27% in placebo [52]	
	No	Primary [55]	Randomized, double-blind study of heavy cannabis users meeting cannabis abuse or dependence criteria who were asked to cease cannabis for 14 days received either bupropion-sustained release (days 1–3, 150 mg once a day; days 4–21, 150 mg twice a day, n = 10 randomized, five completed) or placebo (n = 12 randomized, four completed). Cannabis withdrawal was a primary outcome (MWC). All patients received MET [55]	Small sample size. High attrition (> 50%). No ITT analysis
			There was no statistically significant difference between bupropion-sustained release and placebo on withdrawal scores. Scores on depression (BDI) and anxiety (BAI) inventories did not differ between groups. No significant difference between groups in sleep measures [55]	
Non-benzodiazepine GABA(A) receptor agonist				
Zolpidem -extended release	No	Secondary [57]	Cross-over placebo design. Heavy cannabis users (at least 25 days/month) alternated between *ad libitum* cannabis use (mean 0.8 g per use) and cannabis abstinence (3 days). Extended-release zolpidem (12.5 mg) or placebo was administered at bedtime during abstinence periods. The primary outcome was sleep quality (polysomnography, respiratory	As noted by authors, short withdrawal period (3 days). Non-randomized. Double-blind only to those administering drugs

(Continues)

TABLE 2 (Continued)

Medication	Approved for use in cannabis withdrawal	Primary or Secondary outcome in study	Design and main findings	Limitation and future research
			function, PSQ). Cannabis withdrawal was a secondary outcome (MWC and WDS) There were no differences between extended-release zolpidem or placebo in cannabis withdrawal scores (MWC, WDS). Some features of cannabis withdrawal induced sleep problems (i.e. REM sleep) were improved with medication but some were not (i.e. time spent in different sleep stages, sleep latency), compared to placebo [57]	
	No	Primary [61]	Counterbalanced placebo design; 11 non-treatment-seeking heavy cannabis users (at least three joints daily, 5 days per week) over three 8-day inpatient phases. Participants completed three distinct medication phases always beginning with placebo on day 1 with the following drugs taken daily for 7 days: placebo, 12.5 mg zolpidem alone and 12.5 mg zolpidem with 6 mg total nabilone. Drug order was randomized. Additionally, participants consumed cannabis in the following manner: active cannabis (5.6% THC) on day one; inactive cannabis (0% THC) on days 2-4; active cannabis on days 5-8 as a masure of relapse. Cannabis was provided on day 1 by the experimenter, but during study days 2-8 the cannabis had to be purchased on a per inhalation cost. Mood (non-standard VAS), sleep (non-standard VAS and wrist activity monitor), food intake and body weight reflected some features of cannabis withdrawal [61] Both medications decreased withdrawal-related disruptions in sleep, compared to placebo. Only zolpidem in combination with nabilone decreased withdrawal-related disruptions in mood and food intake, relative to placebo [61]	Small sample. No cannabis withdrawal scale. Mood and sleep scales not standardized. Not randomized
A₂ₐ adrenergic receptor agonists				
Guanfacine	No	Secondary [58]	Open-label, single-arm pilot trial of cannabis-dependent treatment-seeking outpatients (n = 22) [58]. Participants were titrated to maximum tolerable or target dose over a	Small sample size with a low retention rate (~40% of enrolled participants completed the trial) No control condition

Medication of choice

Cannabis withdrawal pharmacotherapy

There are no medications approved to manage the cannabis withdrawal syndrome. Research on MAW has increased during the past 15 years, but remains less developed than for other drugs of abuse.

Nineteen placebo-controlled studies (17 Clinical; two experimental) and one open-label, non-placebo controlled trial have been reported (Table 2). Sixteen were randomized designs. Fewer than half (n = 9) report cannabis withdrawal (or individual cannabis withdrawal symptoms) as a primary outcome and only three recruited more than 50 participants in the medication arm, two of which found a significant benefit from medication over placebo (dronabinol [46], quetiapine [47]). Attrition among the 17 clinical studies was typically greater than a third of the sample.

In the studies that used standardized measures of the cannabis withdrawal syndrome, six reported greater improvement in those given a cannabinoid medication than placebo (dronabinol [46], quetiapine [47], nabiximols [48, 49], gabapentin [50], oral THC [51]). Ten studies did not. This included trials of bupropion [52], FAAH inhibitor PF-04457845 for the majority of the withdrawal period [18], lithium [53], dronabinol and lofexidine [54], bupropion [55], nabiximols [56], extended-release zolpidem [57], guanfacine [58], escitalopram [59] and nabilone [60]. Some medications produced greater reductions in individual symptoms of cannabis withdrawal (e.g. zolpidem extended-release improved some features of sleep [61], nabilone reduced craving and anxiety [62]) than placebo. This was not true in all cases (e.g. divalproex did not reduce irritability, depression and anxiety [63] and topiramate did not improve mood [64]).

The research on medications for MAW in treatment-seeking, cannabis-using populations is limited by the small number and low quality of studies. Larger replication studies are required to test the efficacy of agents that have shown promising results in small studies. MAW largely treats its symptoms with agents known to reduce them, but many of these drugs have not been well studied in people with CUD and their off-label use is of uncertain efficacy and safety.

Medication use in clinical practice

No medications have been shown to be effective in MAW in randomized controlled trials (Table 2). In clinical practice, short-term symptomatic medications have been used for (a) non-specific general cannabis withdrawal syndrome features and (b) for specific withdrawal symptoms (e.g. sleep, nausea, anxiety, appetite stimulation) to improve patient comfort and retention during withdrawal (Table 3). As with all prescribing, a comprehensive medical, medicine and drug and alcohol use history should guide the use and doses of these medications. All medications have side-effects and these need to be balanced against potential benefits from their unknown efficacy in this population.

TABLE 2 (Continued)

Medication	Approved for use in cannabis withdrawal	Primary or Secondary outcome in study	Design and main findings	Limitation and future research
			period of 2 weeks. This was lengthened to 8 weeks due to a greater than expected number of adverse events. Primary outcomes were feasibility (retention and side-effects). Quantity and frequency of cannabis use and withdrawal (MCW-10) were secondary outcomes to establish efficacy	No significant change in withdrawal symptom severity over the duration of the study

BAI = Beck Anxiety Inventory; BDI and BDI-II = Beck Depression Inventory; CBD = cannabidiol; CBT = cognitive behavioural therapy; CWS = cannabis withdrawal scale; HAQ = HAM-A = Hamilton anxiety scale; Hamilton anxiety questionnaire; HSC = Hopkins symptom checklist; ITT = intention to treat; MET = motivational enhancement therapy; MCQ = marijuana craving questionnaire; MCr = marijuana craving report; MOS-SS = medical outcomes study–sleep scale; MWC and MWSC = marijuana withdrawal (symptom) checklist; POMS = profile of mood states; PSQI = Pittsburgh sleep quality index; RCT = randomized controlled trial; REM = rapid eye movement; SIS = Snaith irritability scale; SMHSQ = St Mary's Hospital sleep questionnaire; SSRI = selective serotonin re-uptake inhibitors; STAI = state–trait anxiety inventory; THC = delta-9-tetrahydrocannabinol; VAS = visual analogue scale; WDS = composite withdrawal scale.

TABLE 3 Examples of medication used in clinical practice

General withdrawal features (off-label)	Medications
	• Dronabinol (one positive trial [46])[a] • Nabiximols (two positive trials [48, 56][a] • Gabapentin (one positive trial [50]) • Nabilone [62]
Anxiety and agitation	• Diazepam
Severe tremors	• Diazepam
Nausea/stomach pain	• Metoclopramide • Hyoscine • Promethazine • Non-opioid analgesia (e.g. paracetamol assuming normal liver function)
Psychotic symptoms/ hallucinations	• Antipsychotics (e.g. olanzapine, quetiapine)
Sleep disturbances	• Zolpidem, extended release [61] • Diazepam • Promethazine

[a]May test positive to cannabinoids in drug-testing.

COMPLEX CASES

The case presented in this review reflects a common, complex presentation.

Polysubstance use is common in cannabis users, with alcohol use disorder (OR = 6.0) and nicotine use disorder (OR = 6.2) the most widely co-used substances [27]. Psychiatric comorbidity is also common, with the two most common mental health problems (besides substance use disorders) mood and anxiety disorders [65, 66]. In cannabis use disorder the OR of having any mood disorder is 3.8 and for any anxiety disorder is 2.8 [27].

Presentation

A 48-year-old male presented to a primary care provider with stomach cramps, headache and elevated anxiety symptoms that have prevented him from working for 48 hours. He stated that while he has been off work, he has heard infrequent but multiple unfamiliar voices telling him that he is going to lose his job. The patient reports that he has been having relationship problems with his partner of 15 years, primarily due to his substance use. He ceased all substance use 60 hours prior to the assessment.

Psychosocial history

The patient is currently on sick leave but has a history of stable employment. He is married with no children. There are financial concerns due to time off work.

• Medical history: he reports stomach cramps, headache, irritability/ anger, loss of appetite, some chills and sweating. Previous history of hypertension, disturbed sleep, mild–moderate sleep apnoea; body mass index (BMI) is 35.

• Psychiatric history: currently reports elevated anxiety and a history and previous diagnosis of unipolar depression. Denies history of schizophrenia or psychotic disorders. [Clinician query: cannabis withdrawal-induced psychosis.] Denies thoughts of self-harm.

• Medication: escitalopram 20 mg (non-compliant), captopril 25 mg (non-compliant), continuous positive airway pressure (CPAP) therapy (non-compliant).

Substance use history

The patient reports daily use of cannabis (average 2 g per day, or approximately eight joints), nicotine 15 'tailor-made' manufactured cigarettes per day plus 'spins' loose tobacco with high THC content cannabis plant 'buds'. He reports infrequent use of alcohol (average three standard drinks peer week) and non-prescribed prescription opioids (oxycodone 10 mg when available, typically one tablet per fortnight). The patient states his longest drug-free period occurred 15 years ago for 6 months after meeting his now partner (aged 33 years). He scores 6 on the Alcohol Use Disorders Identification Test (AUDIT) [67], where ≥ 16 is suggestive of alcohol-related problems, 13 on the Severity of Dependence Scale (SDS) [68], where ≥ 3 of 15 is indicative of cannabis-related problems and 10 (range = 0–10) on the Fagerström Test for Nicotine Dependence (FTND [69]), indicating a high level of dependence. He reports no history of significant substance withdrawal.

Withdrawal assessment

Cannabis is commonly used with tobacco [70], and in treatment-seeking cannabis users approximately two-thirds also use tobacco [71]. Tobacco withdrawal symptoms overlap with cannabis withdrawal and may have a similar intensity and time-course [72, 73]. Table 4 outlines the withdrawal features observed in this complex case and possible management. Nicotine replacement therapy (NRT) may be considered during the withdrawal period and post-detoxification if the patient desires to quit nicotine.

The decision to recommend inpatient admission or outpatient withdrawal in this presentation relies upon an accurate assessment of the brief psychotic episodes and their potential impact on the patient's functioning. Withdrawal from other substance use that may increase risk of adverse outcomes (e.g. alcohol other CNS depressants, opioids) is not present. The patient denies suicidal thoughts, but reports dysthymic mood that is typical for him. He states that his cannabis use is heavier at night in an attempt to improve his sleep, and ceasing use has impaired sleep quality. He reports that his partner of 15 years is highly supportive of his cessation attempt and committed to a substance-free relationship.

The patient reported a preference for home detoxification. He attended with his partner, who reports that they can monitor him closely over the next 5 days. The patient consented to attending primary care appointments daily over the next week. The main management approach to consider is a cannabinoid agonist (e.g. nabilone, off-label) that could be slowly titrated upwards. If

TABLE 4 Complex case: observed and self-report symptoms and possible management

Observed and self-report symptoms	Cannabis	Nicotine	Possible management options
Withdrawal scale scores	CWS [25] = 140 (range = 0–190)	MNWS [91,92] = 14 (observer range = 0–16)	Main management approach for cannabis withdrawal syndrome: cannabinoid agonist (e.g. nabilone, off-label)
Nausea, abdominal cramps, muscle aches	++	+	Metoclopramide Non-opioid analgesia Consider dronabinol (specific for nausea and general for cannabis withdrawal)
Headache	++	++	Non-opioid analgesia
Insomnia	++	++	Sleep hygiene, CBT-I Zolpidem, diazepam
Anxiety	++	++	Supportive counselling Diazepam Recommence escitalopram
Psychosis (query cannabis withdrawal-induced)	++	–	Quetiapine
Irritability	+	+	Psychoeducation Diazepam
Aggressive behaviour	+	+	Psychoeducation Diazepam
Restlessness	+	+	Diazepam
Sweating and chills	+	+	Supportive management
Decreased appetite	+	–	Nutrition support Consider dronabinol (specific for appetite and general for cannabis withdrawal)

++ Strong withdrawal feature present; + withdrawal feature present; – withdrawal features not present; CBT-I = CBT-insomnia.

probable cannabis-related withdrawal psychosis persists, inpatient withdrawal is indicated. Quetiapine (atypical antipsychotic) was introduced in this consultation for review over the following 5 days.

The patient and his partner were provided with psychoeducation on: the course and symptoms of withdrawal, exercises to cope with craving, nutrition, hydration, physical exercise and sleep hygiene. Basic skills in relaxation approaches and managing anger and aggressive behaviour were reviewed in the consultation. Admission to a CBT-based outpatient relapse prevention programme was recommended and a referral provided.

POST-DETOXIFICATION PROGNOSIS

In prospective clinical studies in adults [74] and adolescents [5, 75, 76] with CUD the presence and severity of cannabis withdrawal does not predict cannabis use after completion of MAW. However, Davis et al. [5] found that adolescents who met DSM-5 criteria for cannabis withdrawal relapsed to cannabis use sooner than those who did not meet DSM-5 criteria. More studies with larger patient numbers are required to confirm these findings. Regular cannabis users subjectively report that withdrawal symptoms reduce their desire to abstain from cannabis [20, 75].

RELAPSE PREVENTION

No pharmacological approaches have been approved to prevent risk of relapse to CUD during or after MAW [77]. Psychosocial-based interventions are the first-line treatment [77]. The two most effective stand-alone behavioural interventions are cognitive–behavioural therapy (CBT) and motivational enhancement therapy (MET). Both have similar efficacy [78–83]. There is some evidence that combined CBT and MET produces better outcomes than either approach alone [77, 81].

Abstinence-based contingency management (CM) using incentives to motivate and sustain cessation is an effective adjunct to CBT and MET increases rates of sustained abstinence [77, 81]. In the short term (up to 12–14 weeks), combined MET and CBT doubles abstinence rates and reduces consumption by an average of 25% in those who continue to use cannabis, compared to non-active treatment [81]. There is less evidence on efficacy in the longer term (> 9 months) after treatment. Other behavioural interventions for CUD that have been investigated include social support counselling (SS), drug education counselling (DE), relapse prevention (RP), mindfulness meditation (MM) and 12-step mutual help groups. None of these interventions have enough data to support use at this time [77, 81].

Sustained cannabis abstinence is the most effective treatment goal for patients who have a CUD and who have completed MAW

TABLE 5 Low-risk cannabis consumption guidelines

Using lower THC content products

Adopting methods other than inhalation (if inhaling, avoid 'deep inhalation')

Refraining from daily or near-daily or binging on cannabis use

Where available, using legal and quality-controlled cannabis products and devices

If cognitive performance is impaired, temporarily suspending or substantially reducing intensity of use (e.g. frequency/potency)

Abstaining while pregnant or breastfeeding

Avoiding cannabis while driving, using machinery or engaged in other high-risk activities

Exercising caution in combining other psychoactive substances with cannabis use

Avoiding (or adjusting) use in the presence of psychosis, other psychiatric comorbidities and/or a history of substance use disorders

[77]. However, many patients enter treatment with moderation goals and clinicians must adapt their approaches to work effectively with these patients. Reduced use is a common outcome in outpatient studies, but how long these reductions are maintained and whether reduced use improves psychosocial functioning remains unclear. To retain patients with a moderation goal in a therapeutic relationship and reduce the risk of future cannabis related-problems, low-risk guidelines have been endorsed by a number of health jurisdictions (e.g. [84]) and health experts [85] (see Table 5).

Most cannabis users also use other substances [27, 28]. Meta-analyses demonstrate that psychosocial treatments for polysubstance use have weak efficacy compared to single-substance psychosocial treatments [86]. There are insufficient studies to recommend either treating multiple substances sequentially or concurrently. However, a recent meta-analysis found that combined tobacco and/or cannabis interventions had a modest effect on reducing cannabis but not tobacco. These combined interventions did not increase tobacco or cannabis cessation rates [87].

NEW DEVELOPMENTS

The management of substance withdrawal typically includes pharmacological agents which reduce clinically significant withdrawal symptoms. Cannabis does not have any approved medications for MAW, despite a well-recognized and clinically significant withdrawal profile. A number of novel agents have been examined with some promising results (Table 2). This is an important avenue of future research, with some agents showing early efficacy. For this reason, cannabis agonists have been cautiously used 'off-label' for cannabis withdrawal.

The mainstay of cannabis withdrawal management has been psychosocial education, supportive counselling and behavioural therapies. Despite the wide use of these approaches in clinical practice, few empirical studies have been conducted. These approaches need to be evaluated in controlled research settings. Given the heterogeneity of cannabis withdrawal features and substantial individual variations between patients, new developments in the management of cannabis use disorder and withdrawal are likely to include more targeted behavioural approaches (e.g. [77, 88]). The provision of increased on-line and digital approaches to assist patients in managing cannabis withdrawal may improve accessibility and reduce costs, compared to face-to-face health services.

The legalization of non-medical cannabis use in a number of high-income countries has reduced cannabis prices and increased sales of high-potency cannabis products in these jurisdictions [89]. The cannabis industry is lobbying to reduce cannabis taxes, opposing restrictions on maximum THC levels and promoting the sale of high-potency cannabis such as cannabis edibles, oils, extracts and waxes. Although the effects of these changes have not yet been formally evaluated, increased use of high-potency cannabis is likely to increase the risks for CUD and the severity of withdrawal [77]. Public health messaging should include independent information and advice on the risks of using higher-potency cannabis.

AUTHOR CONTRIBUTIONS

Jason Connor: Conceptualization; project administration; supervision. **Daniel Stjepanović:** Conceptualization; data curation. **Alan Budney:** Conceptualization. **Bernard Le Foll:** Conceptualization; data curation. **Wayne Hall:** Conceptualization; supervision.

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