management of cannabis withdrawal

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introduction

Cannabis is the most widely used illicit substance in the world (UNODC, 2006). In the Australian National Survey of Mental Health and Wellbeing, nearly one in 12 Australians had consumed cannabis more than five times in the preceding 12 months, and of those, 21% met criteria for cannabis dependence (Swift, Hall & Teesson, 2001) . While cannabis dependence is recognised in the International Classification of Diseases, 10th Revision (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR), the existence of a specific withdrawal syndrome has been a more highly debated issue (Smith, 2002). While a specific cannabis withdrawal syndrome is not included in the ICD-10 or DSM-IV-TR (*"clinical significance yet to be determined"*), there is growing consensus of the existence and clinical relevance of such a syndrome. A recent review by Budney et al. (2004:1967) concluded that the evidence indicates *"...that a valid and clinically significant cannabis withdrawal syndrome is prevalent in a substantial proportion of heavy cannabis users"*. Although none of the symptoms comprising the proposed withdrawal syndrome are unique to cannabis and are frequently seen in other substance withdrawal syndromes, they are of clinical relevance to many dependent users and their recognition and management by clinicians is an important area for consideration.

The proportion of patients reporting cannabis withdrawal in recent treatment studies has ranged from 50-95% (Budney & Hughes, 2006). Symptoms commonly experienced include sleep difficulty; decreased appetite and weight loss; irritability; nervousness and anxiety; restlessness; and increased anger and aggression. The majority of symptoms peak between day two and six of abstinence and most return to baseline by day 14. Sleep difficulty, anger/aggression, irritability and physical tension have persisted for three to four weeks in some studies (Budney, Moore, Vandrey, & Hughes, 2003; Kouri & Pope, 2000). Strange dreams failed to return to baseline during a 45-day abstinence study (Budney et al., 2003).

Budney and colleagues propose that a specific cannabis withdrawal syndrome be included in the next revision of DSM (see Table 1 for proposed cannabis withdrawal syndrome criteria) (Budney, Hughes, Moore, & Vandrey, 2004). The authors recommend that the presence of four of the criteria listed in Table 1 should constitute a diagnosis of cannabis withdrawal.

Table 1 Proposed cannabis withdrawal syndrome criteria for inclusion in DSM

Common symptoms	
Mood	
	Anger or aggression
	Irritability
	Nervousness/anxiety
Behavioural	
	Decreased appetite or weight loss
	Restlessness
	Sleep difficulties, including strange dreams
Less common symptoms/equivocal symptoms	
Physical	
	Chills
	Stomach pain
	Shakiness
	Sweating
Mood	
	Depressed mood

Reproduced from Budney et al., 2004

Given the inherent bias in treatment seeking samples, for many dependent cannabis users withdrawal may not be a significant hurdle to achieving a period of abstinence. However, even where withdrawal severity is of a similar magnitude to that experienced by people ceasing tobacco use (Vandrey, Budney, Hughes, & Liguori, 2008; Vandrey, Budney, Moore, & Hughes, 2005), withdrawal can of course be a barrier to attaining abstinence. As with other substances, the range and severity of withdrawal symptoms lie on a spectrum and tend to be greater among heavier, dependent users (Budney & Hughes, 2006). It is also probable that cannabis withdrawal discomfort will be greater among people

with psychiatric comorbidity (Budney, Novy & Hughes, 1999), amongst whom continued use is also most harmful (Hall, Degenhardt & Lynskey, 2001).

For many substance dependence problems, the provision of medically assisted detoxification services to address withdrawal symptoms (of sufficient severity or risk to act as a barrier to achieving abstinence) is often the service that is most attractive to patients and may prompt initial treatment seeking. It is possible that the absence of a range of effective interventions for cannabis withdrawal therefore represents a gap in the provision of clinical services which may result in overall lower levels of treatment seeking and engagement.

For a significant proportion of dependent cannabis users the experience of cannabis withdrawal will pose a significant barrier to achieving a period of abstinence (Hart, 2005). It is among this group of patients that specific interventions to manage withdrawal may be required. Given the range of long-term harms associated with chronic cannabis consumption (Moore et al., 2007; Tashkin, Baldwin, Sarafian, Dubinett, & Roth, 2002), assisting cessation of cannabis use may be associated with significant benefits in social functioning, mental health and physical health.

evidence

withdrawal severity

Withdrawal severity is likely to vary widely between individuals and may fluctuate over time depending on the severity of dependence, context of use and cessation, and current life stressors. Factors that may impact upon the severity of cannabis withdrawal are provided in Table 2, although it should be noted that research in this area is lacking as it relates specifically to cannabis withdrawal.

Table 2 Variables likely to affect the severity of cannabis withdrawal

Psychiatric comorbidity including personality disorder
Dose: amount and potency of preparation consumed
Duration of current use
Mode of administration
Past or current other substance use
Expectation
History of aggression or violence, other personality traits
Setting: outpatient withdrawal may be more severe than inpatient withdrawal
Context: voluntary vs involuntary
Support: professional, family, social
Population: more severe in treatment seekers
Rate of withdrawal (gradual reduction or sudden cessation)
Age
Gender

See for example Budney et al., 1999

cannabis withdrawal measures

There is a lack of psychometrically validated scales for the assessment of the symptomatology and severity of cannabis withdrawal. Haney and colleagues, in studies assessing cannabis withdrawal and subsequent medication treatment trials, used a cannabis withdrawal scale adapted from a cocaine withdrawal scale (Haney, Ward, Comer, Foltin, & Fischman, 1999). This scale has not undergone psychometric testing in cannabis using populations. Budney and colleagues developed the Marijuana Withdrawal Checklist (MWC), a 22-item scale exploring the severity of mood, behavioural and physical symptoms of cannabis withdrawal (Budney et al., 1999) (see Table 3). The instrument can be utilised for retrospective accounts of withdrawal severity, or to assess withdrawal severity in a given time period, typically the preceding 24 hours. A four-point rating scale is used (0=no withdrawal; 1=mild withdrawal; 2=moderate withdrawal; 3=severe withdrawal). Revised versions of this scale have been used in subsequent withdrawal studies and clinical trials (e.g. Budney, Hughes, Moore, & Novy, 2001; Budney et al., 2003; Vandrey, Budney, Kamon, & Stanger, 2005; Winstock, Lea & Copeland, 2007, in press). The MWC is yet to be psychometrically validated. The Marijuana Quit Questionnaire (MJQQ) includes a section on cannabis withdrawal

(Copersino et al., 2006). Eighteen withdrawal items are investigated (drawn from the MWC and one other withdrawal study). Participants report whether the symptom was experienced, symptom duration, and any action taken to relieve the symptom. The Nepean Cannabis Withdrawal Scale (THCw-R) is a recently developed instrument that includes both a patient self-report and clinician assessed withdrawal scale (Dawes, 2007). This scale is currently in the process of being psychometrically validated. In summary, there are no psychometrically validated instruments to assess and guide the management of cannabis withdrawal in clinical populations. Until such scales are available, titration of medications against the symptoms most distressing to each patients and medication side effects (notably over sedation) is a sensible, practical approach.

Table 3 Marijuana Withdrawal Checklist (MWC), 22 item version

Items from published studies of cannabis withdrawal	Items associated with other substance withdrawal
Irritability*	Shakiness
Nervousness	Stuffy nose
Depression	Sweating
Anger	Hot flashes
Craving	Feverish
Restlessness	Diarrhoea
Sleep problems	Nausea
Decreased appetite	Muscle spasms
Strange dreams	Chills
Increased appetite	Hiccups
Violent outbursts	
Headaches	

*Rating scale: 0=none, 1=mild, 2=moderate, 3=severe
Reproduced from Budney et al., 1999

psychosocial and psychoeducation interventions

The use of self-help booklets such as the National Drug and Alcohol Research Centre's cannabis brief intervention booklet *Quitting Cannabis?*, and the Manly Drug Education and Counselling Centre's *Mulling it Over* may be useful to support patients in managing withdrawal and craving. *Quitting Cannabis?* recommends a self-help strategy of distracting, delaying, de-catastrophising and de-stressing to manage withdrawal and craving. This approach was drawn from a randomised control trial of brief cognitive behavioural interventions for cannabis users (Copeland, Swift, Roffman, & Stephens, 2001). These issues will be discussed in more detail in the trigger paper addressing psychological interventions in cannabis treatment.

gradual reduction

The gradual reduction of an agonist substance of dependence is typically associated with less severe and clinically significant withdrawal, because of the less abrupt reversal of neuroadaptive changes that a more gradual taper permits. Such an approach underlies most pharmacologically assisted interventions for substance-related withdrawal (e.g., methadone and buprenorphine taper in opiate withdrawal, and benzodiazepine taper for alcohol and benzodiazepine withdrawal) (Alexander & Perry, 1991; Lejoyeux, Solomon & Ades, 1998; NSW Department of Health, 2006). Although there is no evidence in the literature about the effect of gradual dose reduction of cannabis on the severity of withdrawal symptoms, the relatively long plasma half-life of various active cannabis metabolites (typically cited as 1-4 days) (Johansson, Halldin, Agurell, Hollister, & Gillespie, 1989; Wall & Perez-Reyes, 1981) suggests that a gradual reduction in cannabis use would be an effective strategy for people with cannabis dependence, where individuals are able to exert some control over their use or where access to their cannabis is regulated by a third party. This is supported by the apparent clinical utility of oral THC in the management of cannabis withdrawal (Budney, Vandrey, Hughes, Moore, & Bahrenburg, 2007; Haney et al., 2004). Advice on gradual cannabis reduction may include smoking smaller bongs or joints, smoking fewer bongs or joints, commencing use later in the day and having goals to cut down by a certain amount by the next review.

Although it is likely that most people will experience less severe withdrawal if they gradually cut down, for many dependent users efforts at such control may often be unsuccessful. In such cases sudden cessation may be more successful, though its timing in relation to employment, education or parenting responsibilities must be considered. There is some evidence to suggest that inpatient settings may be associated with less severe withdrawal (Budney et al., 2004; Haney et al., 1999). This may provide patients with time away from home and the removal of behavioural cues associated with cannabis use.

pharmacotherapy trials

There are currently no evidence-based pharmacotherapy treatments for cannabis withdrawal. In recent years a number of clinical trials have been conducted investigating the effect of pharmacotherapy treatments for cannabis withdrawal in adult humans (see Table 4). Medications were chosen on the basis of their previous use in the management of mood disorders and other substance withdrawal, and their potential efficacy in the treatment of symptoms common to cannabis withdrawal. Medications investigated have included bupropion (Haney et al., 2001), buspirone (McRae, Brady & Carter, 2006), divalproex sodium (Haney et al., 2004; Levin et al., 2004), lithium carbonate (Bowen, McIlwrick, Baetz, & Zhang, 2005; Winstock et al., 2007, in press), nefazodone (Haney, Hart, Ward, & Foltin, 2003) and oral THC (Budney et al., 2007; Haney et al., 2004). The rationale for using oral THC, a cannabinoid agonist, has been described above.

These studies utilised either a placebo controlled crossover design or an open-label design. Aside from the methodological limitations of open-label designs and crossover designs, these studies share some common limitations. All had small samples and were comprised almost exclusively of males. People with psychiatric comorbidity or other substance use disorders were excluded. Many of the studies involved medication regimes of longer duration than the time course of the majority of cannabis withdrawal symptoms. In addition, the reported studies utilised different withdrawal and other outcomes measures thereby reducing the comparability of different trials. No studies to date have explored variations in individual pharmacogenetics on the potential efficacy of different medications in managing withdrawal. To date no sufficiently large clinical trials have been conducted to support the routine use in clinical practice of any of the medications investigated so far, although the results of the preliminary studies suggest that further research is warranted among some.

Perhaps surprisingly, while benzodiazepines are probably the most commonly prescribed medications for the symptomatic relief of cannabis withdrawal, the efficacy of this drug class in the management of cannabis withdrawal is yet to be investigated in human clinical trials (Hart, 2005). Commonly used in detoxification from alcohol, stimulants and opioids (Baker, Lee & Jenner, 2004; Kosten & O'Connor, 2003), their general calmative, sedative and antispasmodic effects may be useful. Antipsychotic medications have not been investigated as potential therapeutic agents in the management of cannabis withdrawal.

Table 4 Studies that have investigated the effects of pharmacotherapy treatments for the management of cannabis withdrawal in adult humans

Investigators	Design	n	Inclusion criteria	Medication	Daily dose	Duration per condition	Treatment completion (n, %)	Results	Further research required
Haney et al., 2001	Randomised, double-blind, placebo controlled, crossover; outpatient 11 days/ inpatient 17 days	10 (8 male)	Regular cannabis use	Bupropion	300mg	4 weeks	9 (90%)	Ratings of irritability, restlessness, depression and sleep difficulty worsened by bupropion compared to placebo	No
Haney et al., 2003	Randomised, double-blind, placebo controlled, crossover; outpatient 9 days/ inpatient 17 days	11 (8 male)	Regular cannabis use	Nefazodone	450mg	26 days	7 (64%)	Ratings of anxiety and muscle pain reduced by nefazodone but had no effect on other withdrawal symptoms	Some evidence
Haney et al., 2004 [Study 1]	Randomised, double-blind, placebo controlled, crossover; inpatient 15 days/ outpatient 5 days/ inpatient 15 days	11 (all male)	Regular cannabis use	Oral THC	50mg	5 days active; 25 days placebo	7 (64%)	Oral THC reduced ratings of marijuana craving, anxiety, feeling miserable, sleep problems, chills, and increased food intake	Yes
Haney et al., 2004 [Study 2]	Randomised, double-blind, placebo controlled, crossover; outpatient 14 days/ inpatient 15 days	8 (7 male)	Regular cannabis use	Divalproex sodium	1500mg	29 days	7 (88%)	Divalproex reduced marijuana craving but worsened ratings of anxiety, irritability, 'bad effect', and tiredness	No
Levin et al., 2004	Randomised, double-blind, placebo controlled, crossover; outpatient	25 (23 male)	DSM-IV cannabis dependence	Divalproex sodium	1500-2000mg	6 weeks	9 (36%)	Reductions in irritability reported in both the divalproex and placebo condition	No
Bowen et al., 2005	Open-label; outpatient	9 (7 male)	DSM-IV cannabis dependence	Lithium carbonate	600-900mg	6 days	9 (100%)	Four participants reported improvements in withdrawal symptoms they attributed to lithium	Yes
McRae et al., 2006	Open-label; outpatient	11 (10 male)	DSM-IV cannabis dependence	Buspirone	10-60mg	12 weeks	2 (18%)	Significant reductions in marijuana craving, irritability and anxiety at a median 23 days post-baseline	Some evidence
Budney et al., 2007	Randomised, double-blind, placebo controlled, crossover; outpatient	22 (16 male)	Regular cannabis use	Oral THC	Condition 1: 30mg Condition 2: 90mg	5 days	8 (36%)	Low dose oral THC reduced overall withdrawal discomfort, aggression, irritability and sleep difficulty. In addition, high dose oral THC reduced depressed mood and craving	Yes
Winstock et al., 2007, in press	Open-label; inpatient	20 (19 male)	DSM-IV cannabis dependence	Lithium carbonate	1000mg	7 days	12 (60%)	≥6 withdrawal symptoms of at least moderate severity on ≥1 day (n=7). ≥4 symptoms as severe on ≥1 day (n=3). Significant reductions in symptoms of depression and anxiety	Yes

concurrent tobacco use

The majority of cannabis smokers in Australia smoke tobacco either in combination with their cannabis (91%) or separately as cigarettes (43%) (Copeland, Swift & Rees, 2001). Both substances impart a poor prognosis for successful cessation for the other and thus any approach to addressing to the use of cannabis will in most instances appropriately address tobacco (Ford, Vu & Anthony, 2002; Stuyt, 1997; Sullivan & Covey, 2002). All forms of Nicotine Replacement Therapy (NRT) are likely to be of some use among tobacco using cannabis dependent patients regardless of whether they use tobacco independently or in combination with cannabis, although available evidence suggests generally poorer outcomes than among non cannabis users. Interestingly, although one might expect an increase in tobacco consumption during the period of cannabis withdrawal, the limited evidence available suggests this is not the case (Budney et al., 2003; Winstock et al., 2007, in press).

issues in managing withdrawal in special groups

Impact of cannabis cessation on underlying health conditions and/or the efficacy of prescribed medication

People self-medicate with cannabis for a number of medical conditions including HIV cachexia, chemotherapy induced nausea, chronic pain, arthritis, spasticity, and multiple sclerosis (Chong et al., 2006; Swift, Gates & Dillon, 2005). Cessation of cannabis use may leave symptoms associated with these conditions untreated which may be associated with acute exacerbation.

Cannabis has been shown to affect the metabolism of some classes of medication such as antipsychotics (Silvestri et al., 2000), necessitating the prescribing of higher doses in regular cannabis smokers. In such cases cessation of cannabis use may lead to inadvertent toxicity. Examples include induction of P450 isoenzyme CYP 1A, which may impact on the metabolism of clozapine and olanzapine, by tobacco and cannabis (de Leon, 2004).

Chronic pain

Cannabis and its derivatives may be effective analgesics in a range of painful conditions, with particular benefits accrued in those with musculoskeletal/spasm/arthritic disorders such as multiple sclerosis (Chong et al., 2006). For some patients careful consideration will need to be given to providing alternative licit analgesia or other coping strategies before commencing cannabis reduction.

Young people

The very early onset of cannabis use among young people may be a marker for other psychosocial problems and is often seen in conjunction with other substance use or psychiatric disorders (Fergusson, Horwood & Swain-Campbell, 2002; Patton et al., 2002). Aggression and hostility may be particularly common in younger male users with pre-morbid aggressive personalities. This may be a particular issue among people in juvenile detention centres.

depressive symptoms in cannabis users

The incidence of depression and anxiety is higher in people with cannabis dependence than in the general population (Arendt, Rosenberg, Foldager, Perto, & Munk-Jorgensen, 2007; Copeland, Swift & Rees, 2001). Therefore symptoms suggestive of a mood disorder may be a presenting complaint and a specific patient-initiated request for antidepressants may be made of the treating practitioner. However, precipitous prescription and diagnosis should generally be avoided at a first presentation since there are a range of psychological and behavioural symptoms that may be seen in association with the chronic consumption of cannabis that might be interpreted as depression, including low level paranoia and the 'amotivational syndrome'. A significant reduction or cessation of cannabis use may be associated with improvements in ratings of mood, negating a diagnosis of depression and the need for medication. That persistent cannabis intoxication may lead to a presumptive diagnosis of a depressive illness is supported by findings from a recent study of 20 dependent cannabis users enrolled in a withdrawal study, where 85% scored at least moderate scores on the Beck Depression Inventory (BDI-II) (Beck, Steer & Brown, 1996) at baseline but at day 107 follow-up moderate depression scores were persistent in only two participants (Winstock et al., 2007, in press).

In addition to the difficulty of making an accurate diagnosis of a psychiatric disorder in the context of continued cannabis use, compliance is likely to be poor (McLellan, Lewis, O'Brien, & Kleber, 2000). Furthering the initiation of some antidepressants (SSRIs) early in cannabis withdrawal may worsen symptoms, as was the case with buproprion (Haney et al., 2001). Finally, if psychotropic medication is commenced precipitously patients may attribute improvements in mood to medication rather than

the cessation of cannabis use. The motivation for continued abstinence may be removed if patients fail to attribute improvements in mood to the cessation of cannabis use.

recommendations

identification and assessment

Inquiry into drug and alcohol use should form part of any routine assessment with a patient. Although some dependent cannabis users may approach specialist services directly, in many cases it is likely that cannabis use problems will be identified during presentation to another health care professional either incidentally or as part of the presenting complaint, for example within primary care or mental health settings. Once a cannabis use disorder has been identified (see trigger paper on screening and assessment) it will be important to identify the severity, nature and clinical significance of any withdrawal discomfort that has been experienced (see Table 5). Patients may identify withdrawal as a barrier to attaining abstinence either spontaneously or on direct questioning about prior withdrawal experiences. Determining the nature of withdrawal may be assisted in some cases by the use of standardised withdrawal measures. The presence of coexisting physical health problems (e.g. pain), psychiatric comorbidity, and other substance use disorders should also be determined since any intervention aimed at assisting the patient to reduce or cease using cannabis will need to be considered in the context of their use of other substances and prescribed medications. When assessing retrospective accounts of withdrawal discomfort, it is important to identify situational, temporal and other psychosocial variables that may have influenced the withdrawal experience. For example, did the patient quit suddenly, was it voluntary or enforced (e.g., due to incarceration). Corroborative information from family or others close to the patient may also inform the clinical picture as well as highlight the potential effect of withdrawal on people around the individual. Identification of helpful and less useful strategies used during previous attempts should be explored and positive initiatives built upon.

Table 5 Assessing the significance and nature of cannabis withdrawal

- range and severity of individual symptoms (predominant symptoms)
- specific risks of withdrawal to self or others (e.g., violence)
- previous approaches to self-management
- duration of withdrawal
- other substance use/mental health disorders that may affect clinical progression of withdrawal
- prescribed medications (which may exacerbate withdrawal or whose metabolism may be altered on cessation of cannabis use)
- patient expectations and preference
- environmental factors conducive or not conducive to achieving withdrawal – including safety of others

initial advice and harm reduction advice including cutting down

A range of cannabis use reduction strategies exist that can be adopted to support the goal of achieving abstinence from cannabis or a significant reduction in use (Swift, Copeland & Lenton, 2000). For most dependent cannabis users, initial advice should include education on the less harmful ways of consuming cannabis (e.g., reduce daily intake, avoid tobacco, avoid using bongs) and if time, clinical setting or individual circumstances of the person permit, advice to gradually reduce the amount they use over a few days or weeks prior to cessation of use. Whether controlled use of cannabis is a clinically attainable and clinically useful goal for dependent cannabis users has yet to be investigated. Advice should also be provided on avoiding an increase in the consumption of other psychoactive substances, since this may lead to the risk of greater abuse.

concurrent tobacco use

For patients who smoke cannabis and use tobacco independently, there is no evidence to guide clinicians that one should be stopped before the other. For patients who smoke cannabis mixed with tobacco and do not smoke tobacco independently, the advice should be that they cease both simultaneously with the provision of NRT considered. For those patients considering buproprion, clinicians

should take heed of the exacerbating effect of this anti-smoking drug in a trial of its use in cannabis withdrawal (Haney et al., 2001). Thus, if buproprion is considered clinically appropriate in tobacco smoking cannabis users, treatment should be commenced at least 1-2 weeks prior to cessation of both cannabis and tobacco.

pharmacotherapies for cannabis withdrawal

Of the medications investigated in controlled studies, only oral THC has been found to be effective in reducing a broad selection of cannabis withdrawal symptoms. There is evidence of a dose-response relationship between oral THC and reduction of withdrawal symptoms (Budney et al., 2007). Further investigation of oral-THC is required. The results of the open-label trial of lithium conducted by Winstock et al., 2007, in support of an earlier preclinical trial (Cui et al., 2001) and small open-label human pilot (Bowen et al., 2005), provides preliminary evidence of the potential role of this medication in the management of cannabis withdrawal and suggests that a controlled trial of lithium is warranted. Nefazodone and buspirone may benefit from further investigation in controlled studies of shorter duration of dosing than investigated to date, congruent with the time course in which the majority of cannabis withdrawal symptoms would return to baseline (1–2 weeks).

symptoms focused approach

In the absence of a body of published literature or other clinical evidence demonstrating the efficacy of any one class of medication or prescribing schedule over another for the relief of any particular symptom cluster, a menu of prescribing options should be considered using a symptoms focused approach (see Table 6). Importantly, it is recommended that mood stabilisers, antipsychotics and antidepressants are not used for the management of acute cannabis withdrawal. In addition, it is recommended that psychotropic medications are not initiated for the management of psychiatric disorders first diagnosed during a period of dependent use or withdrawal. In those with a well documented pre-existing psychiatric diagnosis requiring for example SSRIs, medication may be commenced after the first few days of withdrawal have been managed, since earlier introduction may worsen symptoms of nervousness and insomnia.

Given the wide interpersonal variability in the experience of withdrawal, dosages and prescribing schedules will most effectively be decided upon *only after* a thorough exploration of the individual patient's symptom profile and circumstances. Most commonly used are a range of medications targeted at providing symptomatic relief, typically involving sedation. In Australia, the most widely used medications are diazepam (or other benzodiazepines) and sedating antihistamines such as promethazine and pericyazine, although there has been no formal evaluation of their effectiveness (Hart, 2005).

For each medication class recommended below (see Table 6), determining the precise therapeutic regime to assist in the management for cannabis withdrawal there are five main considerations:

- timing and duration of any medications during the acute withdrawal period
- relative safety profile of any medications used and the incidence of adverse effects given that the symptoms that are being treated are not life-threatening or typically severe
- abuse liability of any medication prescribed and the ability to safely monitor the use of these medications
- potential for cessation of cannabis use to exacerbate underlying medical or mental health conditions or alterations in the efficacy of other prescribed medications through changes in metabolism

Finally, although the vast majority of patients requiring assistance for withdrawal can be safely and effectively supported in the community, for people dependent on other substances (especially alcohol) or people with psychiatric comorbidity or premorbid aggressive traits, inpatient admission may be appropriate. The inpatient setting may reduce the risk for others who share the patient's home environment.

timing and duration of medication provision

Prescriptions should generally provide 4-7 days worth of medication. Where early side effects are unlikely to exacerbate withdrawal symptoms medications are in most cases most appropriately commenced on the day of cessation. Patients should be advised of potential interactions between prescribed medications and cannabis (e,g., increased sedation) and should be advised to refrain from taking prescribed medications should they continue to consume cannabis. A seven day medication schedule will cover the main period where withdrawal symptoms are of significant severity in the majority of patients. More prolonged symptoms

such as sleep difficulty and strange dreams may be prolonged if anxiolytics are continued beyond 1-2 weeks. Persistent sleep problems related to cannabis withdrawal are more appropriately addressed through non pharmacological approaches such as effective sleep hygiene and relaxation techniques. Medication should only be extended beyond 7-10 days if the patient is reviewed and specific withdrawal symptoms are still present. Consideration should then be given to the possibility that persistent mood symptoms may be reflective of an underlying psychiatric disorder as opposed to cannabis withdrawal. Typically a period of two to four weeks of abstinence from cannabis should pass before a psychiatric diagnosis is made and treatment commenced.

relative safety profile of any medications

Given that cannabis withdrawal symptoms are not dangerous or life-threatening, medications with good safety profiles and few adverse effects are optimally chosen. This would generally exclude most of the common psychotropic classes and high dose sedatives, as well as consideration of the potential interaction with prescribed medications and other substance use.

abuse liability of any medication

Where there are concerns of a patient not taking medication as directed or where there are other concerns regarding the abuse liability of the medication, the doctor should utilise frequent script reviews and short dispensing windows from the pharmacy or outpatient unit to ensure that medication is taken as directed. Review by a practice nurse or an outpatient drug and alcohol specialist may also be beneficial. Benzodiazepines are best avoided in patients with a history of dependence or abuse of alcohol or other CNS depressants and should generally not be provided for more than two weeks.

Table 6 Symptom focused approach to managing cannabis withdrawal

Symptom	Medication	Psychosocial intervention
Insomnia	Benzodiazepines (e.g., oxazepam 30mg o.d, or temezapam 10-20mg o.d), zopiclone (7.5-15mg o.d), zolpidem (10mg o.d) promethazine (25-50mg)	Sleep hygiene advice, stimulant control procedures, Progressive Muscular Relaxation
Irritability, restlessness, nervousness/anxiety	Benzodiazepines (e.g., diazepam 5mg t.i.d)	Meditation, exercise, relaxation techniques, family support and education
Headache, muscular ache, spasms and pain	Paracetamol (1g q.i.d), NSAIDs (e.g., ibuprofen 400mg t.i.d), magnesium	Avoid caffeine and dehydration
Sweating, chills	Paracetamol, appropriate hydration and appropriate clothing	
Nausea, nasal congestion	Antihistamine (e.g., promethazine, 25-50mg) metoclopramide (10mg b.d), prochlorperazine (25mg b.d)	

insomnia and anxiety-related symptoms

As the most commonly used class of drugs in managing substance use withdrawal syndromes, benzodiazepines have a potentially useful short-term (4-7 days) role in assisting with anxiety-related symptoms and insomnia. The prescribing of benzodiazepines should be avoided where there is a high abuse liability, for example to people with other substance use disorders. In such cases alternative night sedation such as promethazine or zopiclone may be used. Night sedation may be all that is required (e.g., diazepam 10mg or temazepam 20mg but where necessary may be supplemented by low doses of diazepam during the day (5mg b.d or t.i.d). Short-term, benzodiazepines may provide effective relief from anxiety and insomnia, but their continued use should be avoided because of risk of abuse and dependence.

Antipsychotics have a number of potentially significant side effects and the only symptomatic benefits they appear to provide in the initial period of their consumption are ones of anxiolysis and sedation - both adequately and safely catered for by judicious use of benzodiazepines. In Australia, atypical antipsychotics if prescribed for the management of cannabis withdrawal are being used off PBS listing. It is recommended that antipsychotics are not routinely used for the management of cannabis withdrawal. Their use during withdrawal in those with underlying psychotic illness of course may be indicated, though dose reduction may be indicated following cessation of cannabis and tobacco.

headache, muscular ache and pain

Simple analgesia and antipyretics such as paracetamol and NSAIDs may be effective.

nausea

A sedating or non-sedating antihistamine or metoclopramide are all appropriate. Promethazine 50mg at night can be an effective sedative but may have persistent sedative effects on waking.

Impact of cannabis cessation on underlying health conditions and/or the efficacy of prescribed medication.

In cases where cannabis is used to self-manage medical conditions including MS and chronic pain, consideration should be given to the commencement of alternative management approaches (whether medication based or not) to support ongoing cessation of use.

In cases where patients prescribed antipsychotic medications cease using cannabis, consideration should be given to reviewing the medication response, and where appropriate, to reducing the dose to avoid the development of toxicity or worsening of side effects such as sedation. This is particularly important in the case of people with schizophrenia who use cannabis and who tend to be on higher doses of neuroleptics.

diagnosing and managing depressive symptoms in cannabis users

It is recommended that complaints of anorexia, insomnia, agitation and hostility in the context of acute withdrawal need to be considered and reviewed after a few days. The diagnosis and initiation of any antidepressant medication should be deferred until after detoxification and withdrawal has subsided. In cases where a patient's clinical history is well known to the treating clinician or where the patient has a well documented primary depressive illness, for example, it would be appropriate to commence an antidepressant (initially at half a dose to avoid early side effects) 1-2 weeks following cessation of cannabis use. Clear advice should also be given to the patient concerning the sudden cessation of antidepressant medication in cannabis users since a discontinuation syndrome associated with cessation of antidepressants may exacerbate cannabis withdrawal or their underlying mental health problems.

summary

Cannabis withdrawal represents a constellation of symptoms that is of clinical relevance in a large proportion of dependent cannabis users. Withdrawal symptoms may be a barrier to attaining abstinence and are likely to be more pronounced in heavy dependent users and in people with underlying psychiatric comorbidity. Appetite and sleep disturbance predominate with symptoms of restlessness, anxiety, aggression and a number of less common moderate physical complaints. Typically lasting 1-2 weeks, the appropriate use of medication when combined with psychoeducation and sleep hygiene may be helpful in minimising discomfort and risks associated with cessation of use. With no evidenced-based pharmacological approach currently identified and no psychometrically validated withdrawal scale available, the default management approach for cannabis withdrawal for most patients should be accurate information provision, psychological support, sleep hygiene advice, nicotine

replacement where indicated and minimal medication provided using a symptoms focused approach. The impact of cessation upon underlying psychiatric and physical conditions should be considered prior to commencing withdrawal management. The diagnosis of psychiatric disorders and the initiation of psychiatric medications at a first presentation should be avoided in order to permit greater diagnostic accuracy, appropriate patient attribution and improved clinical outcomes.

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