Cannabis Withdrawal – A New Diagnostic Category in DSM-5

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ABSTRACT

Background: Cannabis withdrawal was not formally recognized by the DSM-IV classification but is listed, albeit without diagnostic criteria by ICD-10. The American Psychiatric Association recently has included cannabis withdrawal into DSM-5 classification as part of the "Substance-Related and Addictive Disorders" Section. However, many psychiatrists as well as other medical professionals have very little information, if at all, about the new diagnostic entity.

Method: The information was obtained from PubMed (research words: Cannabis, THC, Hashish, Marijuana and Withdrawal). The different clinical symptoms of the phenomena as well as some pathophysiological mechanisms and treatment considerations were summarized and discussed.

Results and Conclusions: A substantial amount of scientific data has been obtained in recent years concerning reliability, validity and clinical importance of cannabis withdrawal. The possible influence of cannabis withdrawal on the severity of major psychiatric disturbances is far from being understood and deserves further research.

Limitations: The reviewed studies varied in sample size, design and methodology limiting clear conclusions.

Drug abuse among psychiatric patients is a widely recognized problem although the precise extent and the origin of this phenomenon are still unclear. In the large-scale CATIE study in the U.S.A., of the 1,460 participants, 23% used substances and 37% of this group met criteria for substance use disorder (1). In Israel the comorbidity level is also substantial – among psychiatric inpatients lifetime prevalence of drug abuse is about 24%, active abuse of drugs (during last month) is 17.3% and 28.2% of this group abuse two or more substances (2). After alcohol and nicotine, cannabis is the most abused substance in the general population and among dual-diagnosed patients (3).

Cannabis withdrawal was not formally recognized by DSM-IV (4) due to uncertainty of the diagnostic features. It is listed, albeit without diagnostic criteria, in the International Statistical Classification of Diseases and Related Health Problems, tenth revision (5).

PREVALENCE AND SYMPTOMS OF CANNABIS WITHDRAWAL

Budney and colleagues provided clear documentation of the present research that supports a compelling argument for the existence of a clinically important cannabis withdrawal syndrome. In their detailed and comprehensive review (6) the authors stated that "designation of a true withdrawal syndrome requires evidence that the negative abstinence effects 1) occur reliably, 2) are not exceptionally rare, 3) have a specific time course that includes a return to baseline state (i.e., are transient effects), 4) abate with readministration of the drug, 5) are due to deprivation of a specific substance, and 6) are clinically significant" (p. 1967). According to these principals it was proposed that "…the cannabis withdrawal syndrome is reliable, valid, and clinically important and should be included in the next revision of DSM" (p. 1775).

Additional evidence has accumulated demonstrating that cannabis withdrawal is not rare in the general population, and indeed is very common in persons seeking treatment for cannabis use problems or among heavy users enrolled in research studies. The studies on the issue used several approaches, including retrospective

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self-report (7), prospective out-patient self-report (8, 9), and prospective inpatient observation (10). Two studies (11, 12) examined the prevalence of cannabis withdrawal symptoms using the U.S. National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) dataset. The results showed that about 29% of those who used cannabis with minimum frequency of three times per week within the past year reported experiencing at least two cannabis withdrawal symptoms within the past year. Among those who had ever used cannabis more than three times per week within last year, 44% reported experiencing at least two cannabis withdrawal symptoms and 34% reported experiencing at least three symptoms.

Another study used retrospective self-report data on subjects' "most difficult" quit attempt without formal treatment. The sample included 384 adult, non-treatment-seeking lifetime cannabis smokers (13). This study assessed prevalence, time of onset, and peak intensity (5-point Likert scale) for 39 withdrawal symptoms. The results indicated that 40.9% of subjects met the DSM-5 cannabis withdrawal proposed criterion (at least 3 of 7 symptoms); 30.0% met the Budney and Hughes (14) 4-symptom criteria (at least 4 of 11 symptoms); and 57.3% met the Budney et al. (15) 2-symptom criteria (at least 2 of 11 symptoms). Requiring only 2 out of 7 symptoms for DSM-5 cannabis withdrawal increased the proportion of subjects with cannabis withdrawal to 57.3%, while requiring 4 of 7 symptoms reduced the proportion to 28.1%. Reducing the DSM-5 symptoms list to six by dropping physical symptoms (reported by 24.7% of subjects) reduced the proportion of subjects meeting the cannabis withdrawal criterion only slightly, from 40.9% to 38.0%. This study had several limitations. Data were obtained by retrospective self-report with no external corroboration; subjects were living in the community, with access to psychoactive substances other than cannabis. There were no significant associations between decreased use of caffeine, alcohol, or tobacco during the attempts to quit and meeting DSM-5 proposed criteria for cannabis withdrawal.

The significance of withdrawal symptoms in risk of relapse into active cannabis use disorders remains unclear. Though cannabis withdrawal has been hypothesized to play a role in maintaining cannabis use in several papers (14, 16), in a follow-up study the results were different (17). Withdrawal symptoms were assessed in 36 subjects seeking treatment for cannabis dependence. Follow-up was performed 26±4 months later, and at this point, the withdrawal symptoms were re-assessed. The following symptoms were significantly elevated after abstinence compared with follow-up: irritability, anger, depression, restlessness, craving, sleep problems, strange dreams, increased appetite, violent outbursts, sweating, hot flashes, chills, and shakiness. Average withdrawal scores at baseline did not differ with gender, age, treatment type, extent of cannabis use, or a lifetime history of anxiety or affective disorders. The authors concluded that while withdrawal symptoms have consistently been found to follow the cessation of cannabis use among subjects with a history of heavy or daily cannabis use, the symptoms may be of limited clinical importance. Other factors hypothesized to play a significant role in increasing the risk of relapse following attempts to quit: social role participation, personality, psychiatric disorders, and age of onset, level of use, severity of dependence, or other drug use.

There were serious limitations in the study. The time-period for withdrawal symptoms at baseline was not specified; relapse was assessed 2–3 years after the baseline interview and it might be argued that the potential significance of withdrawal symptoms is unlikely to be detected at such a late point in time. The authors assessed the withdrawal symptoms retrospectively at both baseline and follow-up.

These as well as other research studies on cannabis dependence and withdrawal were conducted since the publication of the DSM-IV and supported inclusion of cannabis withdrawal as a disorder. They were followed by the announcement of cannabis dependence criteria in the DSM-5 under the chapter on diagnosis of "Substance-Related and Addictive Disorders" (18). The specific diagnostic criteria are:

Inclusion: Requires at least three of the following symptoms, developing within one week of ceasing (or reducing) cannabis use that has been heavy and prolonged.

i. Irritability; anger or aggression
ii. Nervousness or anxiety
iii. Sleep difficulty
iv. Decreased appetite or weight loss
v. Restlessness
vi. Depressed mood
vii. Somatic symptoms causing significant discomfort

Exclusion: If the symptoms are attributable to another medical condition or better explained by another mental disorder, including intoxication with or withdrawal from another substance, do not make diagnosis.

The DSM-5 criteria differ somewhat from several prior proposed diagnostic criteria for cannabis withdrawal

(14, 15, 19). These proposals varied in the content and length of the symptom list and the required number of symptoms. Gorelick and colleagues (13) summarized the differences of proposed symptoms in their comprehensive review. The high diversity of proposed criteria for cannabis withdrawal underlined the need for a more conservative approach.

A 15-item version of the Marijuana Withdrawal Checklist (MWC) (20) lists common as well as less frequently observed cannabis-withdrawal symptoms (items: craving for marijuana, depressed mood, decreased appetite, increased aggression, increased anger, headache, irritability, nausea, nervousness/anxiety, restlessness, shakiness, sleep difficulty, stomach pains, strange dreams, and sweating). Participants rate each item on a 0–3 scale (0 = not at all, 1 = mild, 2 = moderate, and 3 = severe) based on their experience the last time they stopped using cannabis. A composite withdrawal discomfort score (WDS) is created by summing the severity ratings of all 15 items. The internal reliability of this measure was proven as high.

POSSIBLE CAUSES AND MECHANISMS OF CANNABIS WITHDRAWAL

Non-human studies of cessation of marijuana or cannabinoids have provided evidence of a withdrawal response. Abstinence effects of cannabis in animals included aggression, anorexia, biting, bruxism, irritability, hair-pulling, hyperactivity, increased eye contact and gross motor movement, piloerection, reduction in operant responding for food, scratching, shaking, tooth-baring, yawning, and frequent periods of EEG desynchronization (15).

Animal models exhibit both tolerance and dependence following chronic administration of cannabinoids. In rodent brain, downregulation of CB1 (cannabinoid receptor type 1) receptor signaling is thought to underlie tolerance (21). The downregulation is larger and occurs more rapidly in cortical regions, such as hippocampus and cerebellum, than in subcortical regions, such as basal ganglia and midbrain (22). The downregulation is reversible upon abstinence and more rapid in striatum and midbrain than in cortical regions (23).

Inhibitors of endocannabinoid-metabolizing enzymes – fatty acid amide hydrolase (FAAH) or monoacylglycerol lipase (MAGL), the enzymes responsible for the degradation of the endogenous cannabinoid ligands anandamide and 2-arachidonoylglycerol – reduce precipitated withdrawal responses in tetracannabinol (THC) - dependent mice (24). The study of Huang et al. (25) was the first to demonstrate hyperlocomotion as an explicit sign of precipitated THC abstinence in mice. Animal models demonstrated the high degree of plasticity that occurs at the molecular level in various brain regions following chronic cannabinoid exposure (26).

Human research has included laboratory studies of directly observed cannabinoid administration and abstinence. Abstinence from THC causes prominent behavior and affective changes (27). The decrease in mesolimbic dopamine function is considered to play the central role in development of cannabis withdrawal (28). The neuropharmacological mechanism of cannabis dependence may involve interactions of the endocannabinoid system with the dopaminergic and opioid systems (29). Hirvonen et al. (30), using Positron Emission Tomography imaging, showed reversible and regionally selective downregulation of brain cannabinoid CB1 receptors in human subjects who chronically smoke cannabis. Downregulation correlated with years of cannabis smoking and was selective to cortical brain regions. After ~4 weeks of continuously monitored abstinence from cannabis on a secure research unit, CB1 receptor density returned to normal levels. Gorelick and colleagues (31) studied the possibility of development of antagonist-elicited cannabis withdrawal in humans. Ten male daily cannabis smokers received eight days of increasingly frequent 20-mg oral Δ^9-tetrahydrocannabinol (THC) dosages (40-120 mg/d) around-the-clock to standardize cannabis dependence while residing on a closed research unit. On the ninth day, double-blind placebo or 20- (suggested therapeutic dose) or 40-mg oral rimonabant, a CB1-cannabinoid receptor antagonist, was administered. Cannabis withdrawal signs and symptoms were assessed before and for 23.5 hours after rimonabant. The first 6 subjects received 20-mg rimonabant (1 placebo); the remaining 4 subjects received 40-mg rimonabant (1 placebo). Fourteen subjects enrolled; 10 completed before premature termination because of withdrawal of rimonabant from clinical development. Three of 5 subjects in the 20-mg group, 1 of 3 in the 40-mg group, and none of 2 in the placebo group met the pre-specified withdrawal criteria of 150% increase or higher in at least 3 visual analog scales for cannabis withdrawal symptoms within 3 hours of rimonabant dosing. There were no significant associations between visual analog scale, heart rate, or blood pressure changes and peak rimonabant plasma concentration, area-under-the-rimonabant-concentration-by-time curve (0-8 hours), or peak rimonabant/THC or rimonabant/(THC + 11-hydroxy-THC) plasma concentration ratios. The sum-

mary was that prespecified criteria for antagonist-elicited cannabis withdrawal were not observed at the 20- or 40-mg rimonabant doses. These results stand opposite to the results of the above mentioned nonhuman studies (24, 25). This issue remains controversial and needs further clarification.

Recently Verweij et al. (32) estimated the role of genetic and environmental influences on individual differences in cannabis withdrawal. The sample included 2,276 lifetime cannabis-using adult Australian twins. Cannabis withdrawal was defined in accordance with criterion B of the proposed DSM-5 revisions. Cannabis abuse/dependence was defined as endorsing one or more DSM-IV criteria of abuse or three or more dependence criteria. The classic twin model was used to estimate the genetic and environmental influences on variation in cannabis withdrawal, along with its co-variation with abuse/dependence. The results indicated that 11.9% of cannabis users met criteria for cannabis withdrawal. Around 50% of between-individual variation in withdrawal could be attributed to additive genetic variation, and the rest of the variation was mostly due to non-shared environmental influences. Importantly, the genetic influences on cannabis withdrawal almost completely (99%) overlapped with those on abuse/dependence. The researchers concluded that cannabis withdrawal symptoms exist among cannabis users, and that cannabis withdrawal is moderately heritable. Genetic influences on cannabis withdrawal are the same as those affecting abuse/dependence.

TREATMENT

A few studies have examined the effects of dronabinol (oral THC) on the symptoms of cannabis withdrawal. Vandrey and colleagues (33) estimated the dronabinol's dose-dependent ability to suppress cannabis withdrawal and cognitive functions. Thirteen daily cannabis smokers completed a within-subject crossover study and received 0, 30, 60 and 120mg dronabinol per day for five consecutive days. Vital signs and subjective ratings of cannabis withdrawal, craving and sleep were obtained daily; outcomes under active dose conditions were compared to those obtained under placebo dosing. On the fifth day of medication maintenance, participants completed a comprehensive cognitive performance battery and then smoked five puffs of cannabis for subjective effects evaluation. Each dronabinol maintenance period occurred in a counterbalanced order and was separated by nine days of ad libitum cannabis use. The results revealed that dronabinol attenuated cannabis withdrawal in a dose-dependent manner and resulted in few adverse side effects or decrements in cognitive performance.

Lofexidine, an agonist at the alpha2-adrenergic receptor that is used to treat opiate withdrawal was tested both alone and in combination with THC in the treatment of cannabis withdrawal (34). The male volunteers (n = 8), averaging 12 marijuana cigarettes/day, were maintained on each of four medication conditions for seven days: placebo, tetrahydrocannabinol (THC) (60 mg/day), lofexidine (2.4 mg/day), and THC (60 mg/day) combined with lofexidine (2.4 mg/day); each inpatient phase was separated by an outpatient washout phase. The results showed the different effects of THC and lofexidine: reversal of anorexia and weight loss associated with marijuana withdrawal, decrease in subset of withdrawal symptoms, but increase in sleep onset latency, and no decrease in rate of marijuana relapse. Lofexidine was sedating, worsened abstinence-related anorexia, did not robustly attenuate withdrawal, but improved sleep and decreased marijuana relapse. The combined use of lofexidine and oral THC was proposed in cases of cannabis withdrawal.

Effects of baclofen and mirtazapine on a laboratory model of marijuana withdrawal and relapse were also studied (35). During active marijuana smoking, baclofen decreased craving for tobacco and marijuana in a dose-dependent manner, but had little effect on mood during abstinence and did not decrease relapse. Baclofen worsened cognitive performance regardless of marijuana condition. Mirtazapine improved sleep during abstinence, and robustly increased food intake, but had no effect on withdrawal symptoms and did not decrease marijuana relapse. Overall, this human laboratory study did not find evidence to suggest that either baclofen or mirtazapine showed promise for the potential treatment of marijuana dependence.

The efficacy of nefazodone and bupropion-sustained release was also investigated for the treatment of cannabis dependence and withdrawal (36). A double-blind, placebo-controlled, design was employed to assess if nefazodone and bupropion-sustained release increased the probability of abstinence from cannabis and reduced the severity of cannabis dependence and cannabis withdrawal symptoms during a 13-week outpatient treatment program. One-hundred and six participants (mean age= 32 years; females n = 25) were randomized to one of three medication conditions (nefazodone, bupropion-sustained release, or placebo) and participated in a weekly, individually based coping skills therapy program. Results

indicated an increased probability of achieving abstinence over the course of treatment and a decrease in the severity of cannabis dependence and the withdrawal symptom of irritability. There were no significant effects demonstrated for nefazodone and bupropion-sustained release on cannabis use or cannabis withdrawal symptoms. The results indicate nefazodone and bupropion-sustained release may have limited efficacy in treating cannabis dependence.

The different and promising approach in treatment of cannabis withdrawal was raised by Mason et al. (37) who conducted a phase IIa proof-of-concept pilot study to examine the safety and efficacy of a calcium channel/GABA modulating drug, gabapentin, for the treatment of cannabis dependence and withdrawal. A 12-week, randomized, double-blind, placebo-controlled clinical trial was conducted with 50 unpaid treatment-seeking male and female outpatients, aged 18-65 years, diagnosed with current cannabis dependence. Subjects received either gabapentin (1200 mg/day) or matched placebo. Cannabis withdrawal symptoms were assessed using the Marijuana Withdrawal Checklist. Relative to placebo, gabapentin significantly reduced cannabis use as measured both by urine toxicology and by the Timeline Followback Interview. The symptoms as measured by the Marijuana Withdrawal Checklist were also significantly decreased. Overall, gabapentin was associated with significantly greater improvement in overall performance on tests of executive function. This pilot study provided preliminary support for the safety and efficacy of gabapentin for treatment of cannabis withdrawal that merits further study, and provides an alternative conceptual framework of this issue.

CANNABIS WITHDRAWAL IN PATIENTS WITH CO-OCCURRING ADDICTIVE AND MAJOR MENTAL DISORDERS

Cornelius and co-authors (38) reported that cannabis withdrawal is common among treatment-seeking adolescents with cannabis dependence and major depression, and is associated with rapid relapse to dependence and provides support for the clinical significance of withdrawal among dual diagnosed adolescents. The participants in this study included 170 adolescents and young adults, including 104 with cannabis dependence, 32 with cannabis abuse, and 34 with cannabis use without dependence or abuse. All of these subjects demonstrated current depressive symptoms and cannabis use, and most demonstrated current DSM-IV major depressive disorder and current comorbid cannabis dependence. Most (N=80) of those subjects also demonstrated a current diagnosis of major depressive disorder, and a larger number (N=85) demonstrated a lifetime diagnosis of major depressive disorder. The mean number of cannabis withdrawal symptoms in this cannabis dependent group was 6.0 ± 3.6. The mean self-rated Beck Depression Inventory Score in this group was 20.6 +/– 9.2, and the mean Hamilton Depression score was 16.1±8.7. These subjects had presented for treatment for either of two double-blind, placebo-controlled trials involving fluoxetine. Cannabis withdrawal was the most commonly reported cannabis dependence criterion among the 104 subjects in the sample with cannabis dependence, being noted in 92% of subjects, using a two-symptom cutoff for determination of cannabis withdrawal. The most common withdrawal symptoms among those with cannabis dependence were craving (82%), irritability (76%), restlessness (58%), anxiety (55%), and depression (52%). Cannabis withdrawal (in the N=170 sample) was reported to have been associated with rapid reinstatement of cannabis dependence symptoms (rapid relapse). These findings suggested that cannabis withdrawal should be included as a diagnosis in the DSM-5 and has clinical importance in patients with co-occurring addictive and affective pathology . The main limitation of the study is lack of analysis of influence of cannabis withdrawal on severity and course of depressive symptoms.

The data concerning appearance of cannabis withdrawal in patients suffering from schizophrenia are very limited. The only study known to us concerning the dual diagnosed patients (39) has been published recently. One hundred and twenty participants, predominantly African-American (62.5%) and male (76.7%), met inclusion criteria; 20.1% reported that their first regular cannabis use (median age 15 years [range 8-48]) preceded their first psychotic symptoms (20 [4-50] years). Twenty (16.7%) participants met lifetime criteria for cannabis abuse; 98 (81.7%) met surrogate criteria for lifetime cannabis dependence. Withdrawal symptoms were reported by 113 (94.2%) participants, with 74.2% reporting ≥4 symptoms. The most frequently reported withdrawal symptoms were craving for cannabis (59.2%), feeling anxious (52.57%), feeling bored (47.5%), feeling sad or depressed (45.8%), feeling irritable or jumpy (45.0%), feeling restless (43.3%), and trouble falling asleep (33.3%). One hundred and four (92.0%) participants took some action to relieve at least one of their withdrawal symptoms during their index-quit attempt, including 26 (23.0%) participants who reported resuming cannabis use. The conclusion of the study, that

cannabis withdrawal is a clinically significant feature of cannabis use among people with schizophrenia, may serve as a negative reinforcer for relapse. The main shortcoming of the study was its uncontrolled design.

There is high comorbidity between cannabis abuse and anxiety and mood disorders (40). The prominent overlap between cannabis withdrawal and symptoms of anxiety and affective disorders, however, makes it difficult for proper diagnosis and research. This group usually is treated by different kinds of medications (anxiolytics, antidepressants, neuroleptics) with possible influence on severity of withdrawal symptoms. Therefore, it is unclear whether the existing diagnostic tools are able to diagnose the signs of cannabis withdrawal in comorbid patients.

LIMITATIONS

The reviewed studies were heterogeneous in sample size, design and methodology. The studies on cannabis withdrawal in "dual diagnosis" patients (mainly schizophrenia and bipolar disorder) were scarce with very limited data for analysis.

CONCLUSIONS

The reliability, validity and clinical importance of cannabis withdrawal have been proven in recent years. However, many clinical implications of the phenomena are far from being understood, especially in dual-diagnosed patients. The possible influence of cannabis withdrawal on the severity of major psychiatric disturbances and reaction to treatment in these patients deserves greater attention in research and clinical practice.

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