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REVIEW

Cannabis withdrawal and sleep: A systematic review of human studies

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ABSTRACT

Background: Sleep problems during withdrawal from cannabis use are a common experience. The details regarding how abstinence from cannabis impacts sleep are not well described. This article reviews the literature including a measure of cannabis withdrawal and sleep in humans. *Methods:* A literature search using a set of cannabinoid and sleep-related terms was conducted across 8 electronic databases. Human studies that involved the administration of cannabinoids and at least 1 quantitative sleep-related measure were included. Review articles, opinion pieces, letters or editorials, case studies (final $N < 8$), published abstracts, posters, and non-English articles were excluded. Thirty-six publications were included in the review. *Results:* Sleep was frequently interrupted during cannabis withdrawal, although the specific mechanisms of disruption remain unclear. *Conclusions:* Methodological issues in the majority of studies to date preclude any definitive conclusion on the specific aspects of sleep that are affected.

KEYWORDS
Cannabis; insomnia; marijuana; sleep; withdrawal

Introduction

Cannabis is the most commonly used illicit drug, with 3.9% of the global population aged 15 to 64 years reporting cannabis use.[1] Notably, approximately 1 in 10 of those who smoke cannabis will experience symptoms of dependence.[2] Some of these symptoms include developing a tolerance to the effect of use, the desire to stop using but an inability to do so and withdrawal when stopping use. Unlike other illicit drugs, there has been some contention as to whether withdrawal following abstinence should be included among these symptoms of dependence.[3] Indeed, withdrawal was not included in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV).[4] Following a large body of research on cannabis use that has identified a consistent pattern of withdrawal,[3,5–12] this now appears in the fifth edition of the DSM (observed as at least 3 of 7 symptoms: irritability, nervousness, sleep difficulty, decreased appetite, restlessness, depressed mood, and physical symptoms).[13]

Although symptoms of withdrawal are expected to follow abrupt abstinence from long-term cannabis use, the composition of withdrawal and extent to which certain symptoms are experienced are not yet well established. Some recent work on the intensity and timeline of cannabis withdrawal symptoms was recently conducted with 50 dependent cannabis users who stopped using cannabis for 2 weeks under outpatient research conditions. [14] A withdrawal syndrome was reported by 73% of the sample and was predicted by the severity of cannabis dependence such that a higher severity was associated with a greater likelihood of withdrawal. In line with previous studies,[6,15–25] the most commonly reported symptoms of cannabis withdrawal included anger/aggression/irritability and sleep dysfunction. The most distressful withdrawal symptom was trouble getting to sleep.[14] In addition, nightmares and strange dreams was the most commonly reported symptom and was the most intensely experienced (peaking for an average of 1.5 days) but was ranked the 10th most distressing symptom (out of 26).

Although sleep-related problems are among the most consistently reported cannabis withdrawal symptoms, very little else is known about their occurrence and what defines a sleep problem. Moreover, the relationship between cannabis use and its effect on sleep is also not yet well understood in general.[26] That is, the current understanding of the effects of cannabis use on sleep in humans is clouded by mixed findings between studies that typically lack statistical control for confounding factors. Notably, medicinal cannabis use has recently been described to alleviate sleep problems by medicinal users,[27–29] whereas the average cannabis user is at a greater risk of reporting sleep problems compared with non-cannabis users in the community.[30–33] Recognizing the impact of cannabis use and abstinence on sleep is important for both the cannabis user and for health providers. That is, with best evidence knowledge regarding cannabis withdrawal and associated sleep problems, abstinence attempts may prove more successful when sleep problems are assessed and addressed as necessary. In order to clarify these associations between cannabis use abstinence and sleep, we conducted a systematic review of all articles that included human participants and an assessment of sleep during cannabis withdrawal.

Review

Literature search

English language studies on human participants were located through online search of 8 electronic databases (Embase, CINAHL, Cochrane Library/EBM Reviews, MEDLINE, and PsycINFO for published studies and Project Cork, DRUG, and PsycEXTRA for

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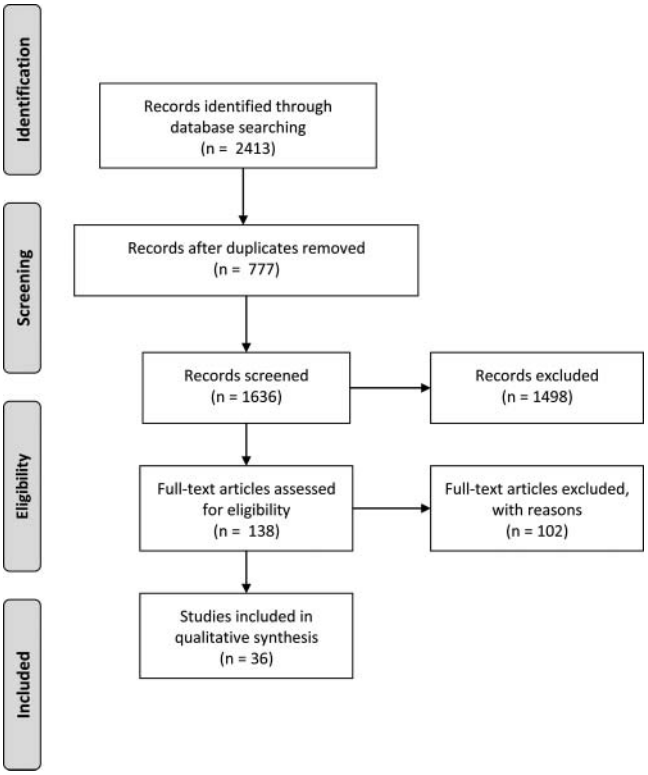

Figure 1. PRISMA flow diagram.[34]

gray literature). The search strategy included the keywords "cannabinoid/s, or, tetrahydrocannabinol, or THC, or cannabis/marijuana" and "sleep, or sleep onset, or sleep apnea, or sleep treatment, or sleep wake cycle, or sleep deprivation, or rapid eye movement (REM) sleep, or non-rapid eye movement (NREM) sleep, or sleep disorder, or insomnia." In addition, we attempted to contact primary investigators who had conducted studies including measures of both cannabis and sleep but did not describe the two in the results of their manuscript. Review articles, posters, qualitative articles, opinion pieces, letters or editorials, case reports (final $N < 8$), and published abstracts were excluded. For purposes of this review, only those articles describing cannabis withdrawal were included (36 studies), whereas those articles involving the administration of cannabis on humans without observing withdrawal and those describing the prevalence of sleep problems among cannabis users and those on associations between use and sleep were excluded (these 102 studies have been previously reviewed elsewhere[26]). This review included all articles current to the end of 2013 and did not exclude studies on the basis of methodological flaws.

Initial searching resulted in 2413 articles being identified, which were independently reviewed by 2 research staff (P.G. and L.A.) in order to remove duplicates and articles meeting exclusion criteria. A consensus was reached, and a total of 777 duplicates and 1600 articles meeting exclusion criteria were removed, leaving 36 relevant articles. These articles were split by those that explored any changes to sleep experienced by those who had already abstained from cannabis use (15 articles),[6,14–24,35–37] and those that explored changes in sleep during withdrawal in an inpatient environment (21 articles).[38–58] In addition, a total of 11 of these 36 articles included data on relapse to cannabis use following withdrawal (see Figure 1).[16,18–20,24,41,46,48–50,54]

Article quality

In order to assess the risk of bias in each article, a custom assessment of article quality and risk of bias was built following suggestions from the Cochrane Collaboration's Risk of Bias Assessment Tool,[59] the Effective Practice and Organisation of Care Review Group Data Collection Checklist,[60] and the assessments of risk of bias by Viswanathan and colleagues.[61] A ratio (reported as a percentage) was calculated to represent which of 38 different factors that the article had adequately addressed compared with the number left unaddressed. As such, a score of 100% was awarded when the article addressed all appropriate risks of bias adequately, whereas 50% was awarded when the article addressed an equal number of risks of bias compared with those left unaddressed. For the purpose of this descriptive review, this risk of bias rating assumes each article design was specifically to assess the impact of cannabis withdrawal on sleep, even though this was rarely the case. As such, the ratings should be considered specific to this review rather than overall article quality.

Results

The proportion of cannabis users who experienced withdrawal and sleep problems during withdrawal

A total of 15 articles investigated the proportion of cannabis users who experienced sleep problems as a part of the withdrawal syndrome, with a collective sample size of 8014 participants (see Table 1 for an overview). The quality of articles was moderate, with scores ranging from 37.9% to 73.3% and an average score of 60.0%. Across studies, the low-quality scores were commonly a result of nonvalidated measures of sleep (typically simple checklists of sleep-related items) and a lack of control for variables that may confound the relationship between withdrawal and sleep (most commonly the frequency, quantity, and duration of cannabis use, other substance use, and preexisting health conditions).

There was an inconsistency as to how many symptoms of withdrawal qualified the diagnosis of a withdrawal syndrome. That is, some studies reported the presence of withdrawal following a single symptom, whereas others required up to 4 or more symptoms. Across studies the proportion of participants that were described to experience withdrawal ranged between 15.6% and 89%, with an average of 57.0%.

A total of 7 articles (6 studies) reported the average number of withdrawal symptoms that were experienced by their respective samples of cannabis users.[6,21,24,35,37,57,58] This number ranged between 1.4 and 9.6, with an average of 5.8 (SD = 2.7). In addition, a total of 9 studies reported the index withdrawal discomfort score from the Marijuana Withdrawal Checklist (referred to as the MWC), a scale developed by Budney and colleagues[37] that gives an numerical indication of the overall severity of withdrawal experienced (although 3 of these studies reported this information in an unclear figure).[18,19,24,35,37,39,41,43,56] These scores ranged between 4.5 (taken from a figure) and 19.7 (out of 28—the most severe), with a mean MWC index score of 9.3 (SD = 5.1).

Across these studies the individuals' withdrawal symptoms relating to sleep included any trouble/difficulty sleeping, waking up early, experiencing "strange" dreams, and sleeping more than usual. The average proportion of participants

Table 1. Articles regarding the proportion of cannabis users who experienced sleep problems during withdrawal.

Author / Year	Quality	Country	Study design	Withdrawal / Sleep measure	Controls	Participants*	Withdrawal outcome and relapse information
Allsop et al. 2011	58.3	Australia	UAU; 15 WD	Cannabis Withdrawal Scale (conducted daily)	1–5	67%, 30.4 (9.6) years; dependent, non-TS ($n = 45$)	73.1% experienced WS: "woke up early" (33%; typically experienced over 0.8 days), "trouble sleeping" (37%; 1.1 days), "nightmares" (41%; 1.5 days), "woke up sweating" (32%; 1.0 day)
Agrawal et al. 2008	73.3	USA	Cross-sectional community survey	Past-year incidence of 4 selected items, e.g., "Sleeping more than usual"	1, 2, 4, 6, 7	62%, 30.8 years; 12.2% dependent, non-TS ($n = 1603$)	43% experienced past-year WS that was predicted by more intense cannabis use, parental substance use problems, and tobacco use. "Sleeping more than usual" (13%), "trouble sleeping" (3.4%), "unpleasant dreams" (5.1%)
Arendt et al. 2007	52.9	Denmark	Longitudinal over 24 months (median FU at 6.5 months)	Experience of sleeping difficulty or strange dreams	7, 8	80.6%, 22.8 (3.6) years; dependent, TS ($n = 36$)	"Sleep problems" (80.6% mild, 63.9% moderate, 41.7% severe) and "strange dreams" (72.2% mild, 55.6% moderate, 27.8% severe) reduced by FU although 67% relapsed
Budney et al. 1999	68.6	USA	Cross-sectional survey of cannabis treatment seekers	Marijuana Withdrawal Checklist	1, 2, 4, 7	85%, 33.8 (8.0) years; dependent, TS, all Caucasian; ($n = 54$)	85% >4 WS: "sleep difficulty" (67% mild, 43% moderate, 19% severe), "strange dreams" (50% mild, 37% moderate, 20% severe)
Budney et al. 2003	65.7	USA	UAU; 45 WD	Sleep Inventory and the Marijuana Withdrawal Checklist	1, 2, 4, 7	66.6%, 30.9 (9.0) years, 36.5 (11.0) years, dependent, non-TS ($n = 18$ current users)	83% ≥2 WS, 78% ≥4 WS. "Sleep difficulty" (61%) increased on withdrawal day 1, peaked day 2, and reduced to baseline levels by day 12. "Strange dreams" (78%) consistently elevated (onset day 2, peak day 9). No effect on sleep time, number of awakenings, or sleep quality. 29% relapsed
Budney et al. 2008	59.4	USA	Cross-sectional survey of cannabis and tobacco users	Withdrawal Symptom Checklist and Withdrawal Discomfort Score	1, 2, 4, 9	59%, 31.9(11.2) years, dependent, non-TS, 66% Caucasian ($n = 67$)	No differences between tobacco and cannabis on WS index or in "sleep difficulty" (≈75% from figure) or "strange dreams" (≈35% from figure). More than half relapsed due to trouble sleeping
Copersino et al. 2006	57.1	USA	Cross-sectional survey of cannabis users past quit attempt	Marijuana Quit Questionnaire	None	78%, 35.0 (11.3) years, 52% white, 78% nondependent users, non-TS ($n = 104$)	32% reported trouble sleeping at 2.74 (3.77) days after quit which lasted 43 (55) days. 19% reported relapse, of those reporting sleep difficulty, 11% relapsed due to these difficulties

(*Continued*)

Table 1. (*Continued*)

Author / Year	Quality	Country	Study design	Withdrawal / Sleep measure	Controls	Participants*	Withdrawal outcome and relapse information
Cornelius et al. 2008	57.1	USA	Cross-sectional survey of cannabis users past quit attempt	Unclear clinical interview	4, 7	54.1%, 20.3 (2.1) years, 70.6% Caucasian, 61.2% dependent, TS ($n = 170$)	68.8% reported WS that was predicted by dependence severity. "Trouble sleeping" (43.7% of dependent users, 2.9% of nondependent users, 31% of total); "vivid unpleasant dreams" (15.5% of dependent users, 0% of nondependent users). Relapse was predicted by >1 WS
Dawes et al. 2011	37.9	Australia	UAU; 5 WD	3 items on sleep difficulty	None	71.5%, 30.5 (8.8) years; dependent, TS ($n = 193$)	Staying awake (62.9% at day 1 then 18.3% on day 5). Sleep disturbance (60.5% on day 1 and 22.9% on day 5). Somnolence (59.3% on day 1 and 19.1% on day 5)
Ehlers et al. 2010	50.0	USA	Cross-sectional survey of cannabis users	Unclear	2, 4	52.4% male, non-TS ($n = 818$)	16.6% experienced WS: "trouble sleeping" (14.9% of those reporting more than 21 occasions of use in 1 year). 16% reported relapse
Hasin et al. 2008	62.5	USA	Cross-sectional community survey	Unclear	1, 2, 4, 5, 7, 9, 10	Weekly cannabis users: 66.9%, 32.6 (1.1) years; 75.4% white % (16.2% dependent) ($n = 2613$); Cannabis-only users: 58.2%, 37.7% aged 18–29 years, 71.1% white (12.9% dependent) ($n = 1119$). All non-TS	57.7% of users / 59.4% of cannabis only users experienced WS, predicted by dependence, dose, depression, personality disorder, and family history. "Insomnia" (6.1% / 6.3%), "hypersomnia" (24.5% / 26.4%), "vivid dreams" (7.4% / 7.0%). Relapse was predicted by WS intensity
Levin et al. 2010	72.0	USA	Cross-sectional survey of cannabis users past quit attempt	Checklist including 8 sleep-related items	7, 11	58%, 31.2 (10.3) years, 79.5% African American, dependent, non-TS ($n = 469$)	42.4% had experienced WS; predicted by being male and by use frequency, duration, and quantity. "Strange dreams" (20.1%), "trouble falling asleep" (46.9%) (trouble falling asleep). Sleep-related WS onset ranged between 2.7 and 6.5 days and peaked at 3.4 days. Symptom severity peaked at 6.3–19.6 days with a duration of 123.8–756.1 days depending on the symptom. 70.4% relapsed; 12%–33.3% relapsed due to sleep problems

Wiesbeck et al. 1996	65.3	USA	Cross-sectional survey of cannabis users	One item on "sleep disturbance"	1, 4	63%, 32 years, 72.2% Caucasian; 50.3% dependent (users reporting >21 past-year occasions of use), all non-TS ($n = 1735$)	15.6% reported >1 WS; predicted by duration and frequency of use. "Sleep disturbance" (13.5% of all users and 75.6% of those reporting WS)
Winstock et al. 2009	61.1	Australia	Inpatient drug treatment exit survey with FU at a mean of 24 and 107 days	Adapted Marijuana Withdrawal Checklist (20 items)	4, 9	95%, 30.05 (7.1) years, 90% nonindigenous Australian, dependent, TS ($n = 17$)	A mean of 4.75 (5.13) WS were reported. At the end of treatment, 100% experienced "Sleep difficulty" (44% as mild, 19% moderate, 38% severe), 50% reported "strange dreams" (reported as 31% mild, 13% moderate, 6% severe). 35% relapsed at first FU and 59% at second FU
Vandrey et al. 2005	58.3	USA	Cannabis treatment intake survey	Marijuana Withdrawal Checklist	5	90%, 16.2 (1.1) years, 89% Caucasian, daily cannabis users (57% dependent) TS ($n = 72$)	An average of 5.3(4.1) WS were reported, 78% >1 WS. 87% experienced "sleep difficulty" (withdrawal symptom was 43% mild, 31% moderate, 13% severe); this symptom correlated significantly with all other symptoms. 49% experienced strange dreams (26% mild, 15% moderate, 8% severe)

Controls: 1 = Age, 2 = Gender, 3 = Substance dependence, 4 = Mental health, 5 = Cannabis use frequency, 6 = Parental substance use, 7 = Other substance use frequency, 8 = Treatment history, 9 = Ethnicity, 10 = Education, 11 = Prescription medications.

UAU = Use as usual; WD = Withdrawal days; WS = Withdrawal symptoms; TS = Treatment seeking; FU = Follow up; NRT = Nicotine replacement therapy.

* For each study the percentage of male participants, participant age (mean [standard deviation]) in years, ethnicity, cannabis use status, treatment seeking status, and total *n* are shown where provided.

Table 2. Summary of articles regarding the proportion of cannabis users who experienced sleep problems during withdrawal.

Author / Year	Had trouble/difficulty sleeping	Had strange/vivid dreams	Woke early or often	Slept more than usual	Any relapsed to cannabis use
		Samples of dependent cannabis users			
Allsop et al. 2011	37.0	41.0	33.0	n/a	n/a
Arendt et al. 2007*	80.6	72.2	n/a	n/a	67.0
Budney et al. 2003	61	78	n/a	n/a	29.0
Budney et al. 1999*	67.0	50.0	n/a	n/a	n/a
Budney et al. 2008	75.0†	35.0†	n/a	n/a	>50.0
Cornelius et al. 2008*	43.7	15.5	n/a	n/a	n/a
Dawes et al. 2011*	62.9	n/a	60.5	n/a	n/a
Levin et al. 2010	46.9	21.8	35.6	27.1	70.4
Vandrey et al. 2005*	87.0	49.0	n/a	n/a	n/a
Winstock et al. 2009*	100.0	50.0	n/a	n/a	59.0
		Samples of nondependent cannabis users			
Agrawal et al. 2008	3.4	5.1	n/a	13.0	n/a
Copersino et al. 2006	32.0	n/a	n/a	n/a	19.0
Ehlers et al. 2010	14.9	n/a	n/a	n/a	16.0
Hasin et al. 2008	6.3	7.0	n/a	26.4	n/a
Wiesbeck et al. 1996	75.6	n/a	n/a	n/a	n/a

* These studies were of cannabis users seeking treatment.
† Taken from an unclear figure.

reporting trouble sleeping was 41.5% (range: 3.4% to 100%; 15 studies); waking up early was 33.2% (range: 31.1% to 35.6%; 2 studies); strange dreams was 34.4% (range: 5.1% to 78.0%; 11 studies); and more sleep than usual was 10.9% (range: 8.7% to 13%; 2 studies). In summary, those reporting any sleep-related symptom of withdrawal ranged between 3.4% and 100%, with an average proportion of 36.9% (see Table 2 for details).

The impact of cannabis abstinence on sleep

A total of 20 studies (21 articles) investigated the impact of abstinence from cannabis use on sleep, with a collective sample size of 511 participants (see Table 3 for details and Table 4 for a summary). The quality of articles was low to moderate, with scores ranging from 32.4% to 80.0% and an average score of 58.4%. Across studies, the low-quality scores were commonly a result of a lack of control for variables that may confound the relationship between withdrawal and sleep (most commonly age, gender, and preexisting health conditions), small sample sizes (with a resulting loss of statistical power), and an unclear reporting of methods. The majority of these 20 studies (21 articles) employed objective measures such as electroencephalogram or movement monitors,[38,40,42,43,45,47–50,55,57,58] whereas a minority employed subjective measures such as validated scales or sleep diaries,[39,51–54,56] and 3 studies did not employ sleep-specific measures.[41,44,46] The total time spent asleep, the number of nighttime awakenings, sleep latency, and an overall measure of "trouble" or "difficulty" sleeping were the most commonly investigated aspects of sleep.

In addition, the effect of cannabis dose prior to withdrawal was investigated in 7 studies (6 articles).[45,47,49–52] The impact of cannabis dose on sleep in withdrawal was inconsistent. In summary, 2 studies did not find a significant effect of oral THC dose,[47] or of THC cigarettes,[52] whereas 2 studies reported that, in comparison with withdrawal following lower doses, the larger doses were associated with greater sleeping difficulties.[45,51] In addition, the dose effect from cannabis was unclear in 3 further studies, as sleep outcomes were affected by the use of medications designed to attenuate cannabis withdrawal, including baclofen (a γ-aminobutyric acid GABA receptor agonist)[49] and mirtazapine (an antidepressant)[49] and lofexidine (a noradrenergic inhibitor).[50] Notably, to reduce any confounding effects on the included data in this review, we consider only those results from the placebo medication arm of these studies.

Across studies, withdrawal was somewhat consistently associated with an increased number of participants reporting "disturbed sleep" or "difficulty sleeping" (observed in 9 studies[38,40,41,44,47–49,51,53]). These difficulties were seen to decrease over time in the longest withdrawal study of 28 days,[44] although 2 studies did not find a significant effect.[50,52] In addition, there appeared to be an inconsistent decrease to sleep efficiency (4 studies [5 articles],[40,45,49,57,58] with 3 studies showing no significant effect[42,49,55]) and sleep quality (3 studies [4 articles],[39,40,45,56] with no effect in 2 studies[43,47]).

Abstinence from cannabis use had less consistent effects on aspects of sleep continuity. The most consistent effect was a likely decrease to the total time spent sleeping during withdrawal from cannabis use (a total of 9 studies reported a decrease,[38–40,48,51,53,54,57,58] whereas 7 studies reported no change[42,43,47,50,52,55,56]). The results regarding number of nighttime awakenings were less consistent (a total of 5 studies [6 articles] reported an increase,[38,40,45,48,49,58] whereas 8 studies did not find a significant effect[39,42,43,49,52,54–56]). Effects on sleep latency were also inconsistent (a total of 6 studies [8 articles] showed an increase,[40,45,46,49,50,54,57,58] whereas 5 studies did not find a significant effect[39,43,49,52,55,56]). Finally, sleep satisfaction did not appear to be significantly affected (2 studies showed a decrease,[51,57] whereas 4 studies reported no significant effect[38,50,52,54]).

Aspects of sleep architecture were less likely to be investigated in the literature and results were mixed. This includes periodic body movements and eye movements (increased in 2 studies [3 articles],[55,57,58] with no effect in 1 study[54]). In addition, results regarding time spent in stage 1 sleep were mixed (1 study showed a significant decrease in time,[40] and 2 studies did not report a significant effect[42,55]), as was stage 2 sleep

Table 3. Articles regarding the impact of cannabis abstinence on sleep architecture.

Author / Year	Quality	Country	Study design	Sleep measure	Control	Participants*	Withdrawal outcome and relapse information
Bolla et al. 2008	77.1	USA	UAU + 2 WD; drug-free control	EEG readings, Horne-Ostberg morningness-eveningness scale; Sleep History Questionnaire, Apnea-Hypopnea Index	1, 2, 4, 7, 10, 11, 12	65%, 21 years, daily cannabis users (29% were dependent) non-TS ($n = 17 + 14$ controls)	No group differences at baseline. Sleep satisfaction ⇩ on night 1; SWS and TST ⇩ on nights 1 and 2 (no longer significant when controlling for IQ), PLM ⇧ on night 1. Sleep efficiency and latency to REM ⇩ and latency ⇧ on night 2. No effect on REM time, WASO, or morningness
Bolla et al. 2010 (extension of Bolla et al. 2008)	80.0	USA	UAU + 14 WD; baseline comparison	EEG readings, Horne-Ostberg morningness-eveningness scale; Sleep History Questionnaire	1, 2, 4, 5, 7, 11, 12	72%, 21.1 (3.1) years, daily cannabis users (27% were dependent) non-TS ($n = 18$)	TST, REM time, and sleep efficiency ⇩ throughout; SWS ⇩ by night 8; WASO and PLM ⇧ by night 13 (more PLM with greater duration of use). No effect on sleep satisfaction
Budney et al. 2001	61.1	USA	UAU + 4 WD, then 5 days UAU + 4 WD	Sleep Inventory (5 items on 7-point Likert scales) and the Marijuana Withdrawal Checklist (assessed at 4 points)	4, 7	58.3%, 30.1(9.0) years, 83.3% Caucasian, 92% dependent, non-TS ($n = 12$)	Sleep quality ⇩, sleep difficulty decreased and returned to baseline; strange dreams ⇧. No effect on TST, number of WASO, sleep latency, or time of WASO
Cohen-Zion et al. 2009	58.3	USA	UAU + 28 WD with drug-free control comparison	EEG readings, Apnea-Hypopnea Index	1, 2, 4, 9, 12, 13	69%, 18.3 years, non-TS ($n = 29 + 20$ drug-free controls)	SWS% ⇩ on night 2 and PLM ⇧ on night 28 only. No effect on TST, REM, S1 or S2, WASO, sleep efficiency, or sleep latency. 31.0% relapsed to any drug use including but not limited to cannabis
Cooper et al. 2013	61.1	USA	800 mg, 6.2% THC dose + 3 WD then 4 dosed nights (with and without quetiapine)	Hours of sleep (self-report) and wrist movement recording (utilized for sleep latency only)	4, 7, 11	87.5%, 26.0 (4.0) years, "regular" users, non-TS ($n = 20$)	TST ⇩ and sleep latency ⇧ during withdrawal with no effect from quetiapine (timeline of the changes was not reported). Withdrawal with quetiapine showed ⇩to TST and latency compared with baseline. Otherwise, no effect on time awake, WASO, PLM, clear headedness, or satisfaction. 20% relapsed after an average of 1.7 (0.3) days withdrawal (no effect shown when on quetiapine)
Haney et al. 2001	58.3	USA	Dosed with 5 2.8% THC cigarettes daily for 4 days + 12 WD (with and without active drug bupropion) with placebo comparison	St. Mary's Hospital sleep questionnaire (index and hours of sleep) and Marijuana Withdrawal Checklist (Craving item only)	4, 7, 14	80%, 27.0 (4.0) years, 20% Caucasian, all daily cannabis users, 90% tobacco smokers, non-TS ($n = 9$)	Sleep time ⇩ and "difficulty sleeping" ⇧ during the first 6 days of withdrawal compared with placebo (more so when on bupropion). Craving was reduced by bupropion

(*Continued*)

Table 3. (*Continued*)

Author / Year	Quality	Country	Study design	Sleep measure	Control	Participants*	Withdrawal outcome and relapse information
Haney et al. 1999a	58.3	USA	Dosed with 4 THC capsules per days for 4 days (20mg then 30 mg THC) then 4 WD with placebo comparison	St. Mary's Hospital sleep questionnaire (reported 3 items only) and Marijuana Withdrawal Checklist	4, 7, 14	50%, 24.7 (3.5) years, 41.7% Caucasian, daily cannabis users, 75% tobacco smokers, non-TS ($n = 12$)	"Trouble sleeping" ⇧ during first day of administration of 30 mg THC only and again on fourth day of withdrawal only. Sleep time and "slept well" did not change during drug administration but ⇩ during days 2—4 of withdrawal. No effect on the withdrawal checklist
Haney et al. 1999b	54.3	USA	Dosed with 4 THC cigarettes per day for 4 days (1.8% and 3.1% THC) then 4 withdrawal nights with placebo comparison	St. Mary's Hospital sleep questionnaire and Marijuana Withdrawal Checklist	4, 7, 14	100%, 25% Caucasian, aged 28 (21–44) years, daily cannabis users, 75% tobacco smokers, non-treatment seekers ($n = 12$)	No effect on self-reported TST and WASO, "slept well", "trouble sleeping", and sleep latency for either dose. No effect on the withdrawal checklist
Haney et al. 2008	65.7	USA	Dosed with 6 cigarettes (3.3% THC) + 3 WD, then 4 days of self-administration, then 4 days with the initial dose. Completed 4 times, first with lofexidine during days 2–8 then combined with 60 mg oral THC, then with placebo	Nightcap objective monitoring and unclear questions on sleep satisfaction and sleep latency	4, 7, 14	100%, 29.0 (7.0) years, 100% non-Caucasian (50% black, 37.5% Hispanic, 12.5% mixed) daily cannabis users, 75% tobacco smokers, non-TS ($n = 8$)	No effect on TST, sleep satisfaction or falling asleep easily was observed between placebo and THC alone during withdrawal. Sleep latency ⇧ on THC alone. Time asleep and sleep satisfaction ⇧ and sleep latency ⇩ on THC + lofexidine compared with placebo. 75% relapsed on placebo and THC conditions, 50% relapsed on THC + lofexidine *No comparisons were made between drug administration and withdrawal periods
Haney et al. 2010	60.0	USA	Dosed with 6 3.3% THC cigarettes per day with Baclofen for 4 days then 4 WD then 4 days of self-administration of THC, repeated but with 6.2% THC cigarettes with mirtazapine	Visual analogue scales on "slept well, woke early, fell asleep easily, feel clear-headed, woke up often, satisfied with sleep." "Actiwatch" was used to measure motor activity in mirtazapine condition only	4, 7, 14	Baclofen condition: 100%, 29.0 (6.0 years, 30% Caucasian ($n = 13$) mirtazapine condition: 100%, 27.0 (5.0) years, 27.2% Caucasian ($n = 12$) all participants were daily cannabis users, "over half" were tobacco smokers. All non-TS	Baclofen condition: No effect on sleep ratings during cannabis administration or withdrawal, except "woke up early" ⇧ during withdrawal. 40–50% relapsed Mirtazapine condition: (objective measure) during withdrawal participants sleep latency, and early awakenings ⇧ whereas efficiency ⇩. (Sleep ratings) during withdrawal "slept well" ⇩ and "woke early" and "woke often" ⇧. These ratings were lessened when on mirtazapine compared with placebo. 64% relapsed

Haney et al. 2013	61.1	USA	One day with 5.5% THC cigarette, then 3 days placebo, then 4 days with access to 5.5% THC cigarettes; this was done with UAU then again quitting tobacco smoking in the week prior	7-item VAS, Nightcap and Actiwatch Activity Monitoring Systems	4, 7, 10, 11	Cannabis smokers (group A): 90.2%, 28.0 (7.0) years, 13.7% Caucasian, non-TS ($n = 51$) Cannabis, and ex-tobacco smokers (group B): 86.7%, 30.0 (6.0) years, 13.3% Caucasian ($n = 15$)	TST, "slept well" and "fell asleep easily" ⇩ and WASO ⇧ during withdrawal in both conditions. Tobacco quitters had more WASO. Objective measure results were unclear. 93% of tobacco smokers and 87% of ex-smokers relapsed to cannabis use (review of past studies found sleep latency was a predictor of severity of relapse among those who relapsed)
Haney et al. 2013	76.3	USA	One day on 5.6% THC cigarettes smoked 6 times (3 puffs), then 3 WD, then 4 days with access to self-administer cigarettes. All completed on placebo, 6 mg/day, and 8 mg/day nabilone	7-item VAS and Actiwatch measuring sleep efficiency (time asleep as a percentage of time with lights out)	3, 4, 11	72.7%, 30.0 (10.0) years, 18.2% Caucasian, daily cannabis users, non-TS ($n = 11$)	TST and "slept well" ⇩ "woke often" ⇧ compared with baseline. These effects were reversed on nabilone dose. "Fell asleep easily" and sleep satisfaction and sleep efficiency did not significantly change during withdrawal, however; all ⇧ on nabilone dose. Self-administration of cannabis was reduced by nabilone dose compared with placebo
Jones et al. 1976	56.8	USA	Increasing dose up to 210 mg THC as either 2.2%, 29% or 96% THC capsules (with 2.8% CBD and 1.5% CBN) over 5–21 days then placebo for 4–9 days placebo (100 mg CBD was used as placebo)	EEG recordings and staff observations	7	100%, 25 (21–31) years, at least twice weekly cannabis users, non-TS ($n = 47$; for REM data $n = 7$ and was excluded)	TST and sleep quality initially increased then returned to baseline during cannabis administration and no change reported during withdrawal. REM and eye movements increased during withdrawal. "Little change" in S4 during withdrawal. "Wild dreams" increased during withdrawal (0% to 19%). "Disturbed sleep" initially decreased during administration (28% to 4%) then increased in withdrawal (to 89%). No dose effect was found and data was collapsed
Mathers and Ghodse 1992	45.9	UK (London)	Survey conducted 1 week into treatment for psychosis then again at 1 and 6 months	Present State Examination	7, 11, 13	Cannabis users with psychosis: 80.3%, 27.0 (7.0) years, 45.9% Caucasian ($n = 61$); nonusers with psychosis: 58.1%, 37.0 (11.0) years, 76.7% Caucasian (n = 43)	A greater proportion of users had "delayed sleep" at 1 month compared with nonusers, but the proportion was not significantly different at intake or 6 month interviews (Caucasians reported delayed sleep and early-morning awakenings more often

(*Continued*)

Table 3. (*Continued*)

Author / Year	Quality	Country	Study design	Sleep measure	Control	Participants*	Withdrawal outcome and relapse information
							compared with Afro-Caribbeans). 63.9% abstained from cannabis use during treatment
McClure EA et al. 2012 (Extension of Vandrey et al. 2011)	45.1	USA	Self-administered cannabis (12 [5] cigarettes on average) over 2 days then 3 withdrawal nights (unclear administration of active drug zolpidem during withdrawal)	Pittsburgh Sleep Quality Index (PSQI), "Embla N-7000 digital PSG data recorder"	4, 5, 7, 12	85%, 29.0 (8.0) years, 25% Caucasian, daily cannabis users (50% dependent) and 80% tobacco smokers, non-TS ($n = 20$)	Sleep efficiency ⇩ with total volume per cigarette and average volume per puff and years of frequent use. Sleep latency ⇧ with total volume and average puff duration and years of frequent use. WASO ⇧ with total volume per cigarette and maximum puff duration. Sleep quality and morning mood ⇩ with maximum puff duration ⇩
Milin et al. 2008	48.3	Canada	UAU prior to entry into treatment for cannabis use, then weekly assessment of withdrawal over 4 weeks	Cannabis Withdrawal Scale	4, 7	66%, 17 years, daily cannabis users all dependent, TS (n = 21)	Sleep difficulties ⇧ steadily over 4 weeks. Index of overall withdrawal syndrome intensity was not related to the quantity of cannabis used, frequency of use, length of dependence, age of onset of daily use, or psychiatric problems
Penetar et al. 2012	43.2	USA	UAU + 14 WD randomized to be with or without active drug bupropion	Daily sleep log and the Stanford Sleepiness Scales; Wrist actimeter was used but data not provided	3, 4, 7	56%, 31.2(9.6) years, 78% dependent, TS ($n = 9$)	No effect on TST, sleep latency, sleep quality, daytime alertness, and number of WASO
Pranikoff et al. 1973	32.4	USA	UAU + 2 WD drug-naïve comparison	EEG readings and unclear sleep survey	7	100%, cannabis users (frequency unclear) non-TS ($n = 40$; of which 20 were nonsmoker controls)	No effect on TST, sleep efficiency, REM time, S1 or S3 time or WASO. S2 time, and sleep latency to S2, 3, and 4 ⇩, S4 time ⇧
Vandrey et al. 2008	51.6	USA	9 days UAU (3.8 [2.1] joints/day) + 5 WD, then 9 days UAU tobacco (20.3 [8.7] cigarettes/day) + 5 WD then 9 days UAU both concurrently + 5 WD	Marijuana Withdrawal Checklist	4, 7, 11	50%, 28.2(10.0) years, daily tobacco and cannabis users, non-TS ($n = 12$)	Sleep difficulty ⇧ for concurrent tobacco and cannabis use on days 2 and 4 of withdrawal, whereas cannabis was not significantly different to tobacco alone. Strange dreams ⇧ for cannabis use and concurrent tobacco and cannabis use, but not tobacco only during withdrawal. 28.6% failed to achieve the required abstinence (reason unclear)

Vandrey et al. 2011	80.0	USA	2 days UAU (access to 0.8 g 3% THC cigarettes) + 5 WD on placebo and again on zolpidem	Pittsburgh Sleep Quality Index, "Embla N-7000 digital PSG data recorder"	4, 5, 7, 12	85%, 29.0 (8.0) years, 25% Caucasian, daily cannabis users (50% dependent) non-TS (n = 20)	TST, S1 and S2 percentage time, sleep efficiency, REM latency ⇩. REM percentage time, sleep latency, and strange/wild dreams ⇧. A significant interaction (cannabis use × zolpidem) was found where WASO ⇧ and sleep quality ⇩ during placebo-abstinence compared with other study conditions. No effect on SWS
Vandrey et al. 2013	51.6	USA	5 days UAU (access to 0.8 g 3% THC cigarettes) + 5 WD on placebo and again on dronabinol (30, 60, and 120 mg)	Sleep diary recordings for sleep latency, TST and WASO + 100-point VAS on sleep quality, mood and alertness on awakening	4, 7, 11	92.3%, 34.0(9.0) years, 100% African American, daily cannabis users (84.6% dependent) non-TS (n = 13)	TST, mood and alertness on awakening and sleep quality ⇩ and sleep difficulty ⇧ during placebo withdrawal. No effect on WASO, strange dreams, or sleep latency. Dose effects were found: 120 mg suppressed mood and alertness to a greater extent compared with 30 mg and placebo; 120 mg suppressed sleep quality compared with 30 mg; 60 mg suppressed sleep quality and mood on awakening compared with 30 mg

Note. Controls: 1 = Age, 2 = Gender, 3 = Substance dependence, 4 = Mental health, 5 = Cannabis use frequency, 6 = Parental substance use, 7 = Other substance use frequency, 8 = Treatment history, 9 = Ethnicity, 10 = Education, 11 = Prescription medications, 12 = Preexisting sleep conditions, 13 = Socioeconomic status, 14 = Body mass index.

UAU = Use as usual; WD = Withdrawal days; WS = Withdrawal symptoms; TS = Treatment seeking; FU = Follow-up; NRT = Nicotine replacement therapy; PSG = Polysomnograph; EEG = Electroencephalogram; PLM = Periodic limb movements; REM = Random eye movement; S1–S4 = Stage 1 to stage 4 sleep; SWS = slow-wave sleep; THC = Tetrahydrocannabinol; TST = Total sleep time; WASO = Wake after sleep onset; VAS = Visual analogue scale.

* For each study, the percentage of male participants, participant age (mean [standard deviation]) in years, ethnicity, cannabis use status, treatment seeking status, and total n are shown where provided.

Table 4. A summary of studies regarding the impact of cannabis abstinence on sleep.

Study	Trouble/difficulty sleeping	Sleep efficiency	Sleep quality	Total sleep time	Sleep latency	Sleep satisfaction	Waking early or often	Periodic limb movement	Stage 1 sleep	Stage 2 sleep	Slow-wave sleep	REM	REM latency	Relapsed to cannabis use
Samples of dependent cannabis users														
Budney et al. 2001	n/a	n/a	⇩	—	—	n/a	—	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Cohen-Zion et al. 2009	n/a	—	n/a	—	—	n/a	—	⇧	—	—	⇩	—	n/a	31.0[†]
Cooper et al. 2013	n/a	n/a	n/a	⇩	⇧	—	—	—	n/a	n/a	n/a	n/a	n/a	20.0
Haney, Bedi et al. 2013	⇧	n/a	n/a	⇩	n/a	n/a	⇧	n/a	n/a	n/a	n/a	n/a	n/a	87.0–93.0[‡]
Haney, Cooper et al. 2013	⇧	n/a	n/a	⇩	n/a	—	⇧	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Haney et al. 2010 (study 1)	—	—	n/a	n/a	—	n/a	⇧	n/a	n/a	n/a	n/a	n/a	n/a	40.0–50.0
Haney et al. 2010 (study 2)	⇧	⇩	n/a	n/a	⇧	n/a	⇧	n/a	n/a	n/a	n/a	n/a	n/a	64.0
Haney et al. 2008	—	n/a	n/a	—	⇧	—	n/a	n/a	n/a	n/a	n/a	n/a	n/a	50.0–75.0
Haney et al. 1999a	⇧	n/a	n/a	⇩	n/a	⇩	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Haney et al. 1999b	—	n/a	n/a	—	—	—	—	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Haney et al. 2001	⇧	n/a	n/a	⇩	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Milin et al. 2008#	⇧	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Penetar et al. 2012#	n/a	n/a	—	—	—	n/a	—	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Vandrey et al. 2008	⇧	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	28.6
Vandrey et al. 2011; McClure et al. 2012	⇧	⇩	⇩	⇩	⇧	n/a	⇧	n/a	⇩	⇩	—	⇧	⇩	n/a
Vandrey et al. 2013	n/a	n/a	⇩	⇩	—	n/a	—	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Samples of nondependent cannabis users														
Bolla et al. 2008; 2010	n/a	⇩	n/a	⇩	⇧	⇩	—	⇧	n/a	n/a	⇩	⇩	⇩	n/a
Jones et al. 1976	⇧	n/a	—	—	n/a	n/a	n/a	n/a	n/a	n/a	—	⇧	n/a	n/a
Mathers and Ghodse 1992	n/a	n/a	n/a	n/a	⇧	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	63.9
Pranikoff et al. 1973	n/a	—	n/a	—	n/a	n/a	—	n/a	—	⇩	⇧[*]	—	⇩	n/a

[#] These studies were of cannabis users seeking treatment for their cannabis use.
[*] No effect on stage 3 sleep, although stage 4 sleep increased.
[†] A total of 31% relapsed to any drug use, including but not limited to cannabis use.
[‡] Data for this study came from 5 previous studies on a variety of cannabis withdrawal medications and included only ex-tobacco and current tobacco smokers.

(2 studies showed a significant decrease,[40,42] although 1 study did not report a significant effect[55]) and slow-wave sleep (2 studies [3 articles] reported a decrease,[55,57,58] 1 study reported that there was no effect on stage 3 sleep, although stage 4 sleep increased,[42] and 2 studies did not report a significant effect on slow-wave sleep[40,47]). A total of 5 studies included REM in their measures, with mixed results (1 study showed a decrease in REM time at night 13 of abstinence,[58] 2 studies showed an increase,[40,47] whereas a further 2 studies showed no significant change[42,55]). Finally, 3 studies investigated the latency to REM sleep and all 3 found a significant decrease during cannabis withdrawal.[40,42,57]

Withdrawal and relapse to cannabis use

A total of 11 articles gave the proportion of participants involved in a study of cannabis withdrawal that reported relapse to cannabis use.[16,18–20,24,41,46,48–50,54] The reported proportion relapsing to cannabis use ranged between 16% and 93%, with an average of 51.4%. Notably, the severity of withdrawal was identified to be a significant predictor of relapse in 2 studies,[15,21] although no association was found in 2 further studies.[18,48]

A total of 3 studies reported the percentage of participants reporting relapse due to sleep-related problems of withdrawal.[16,19,20] One study cited that "more than 50%" of the sample reported sleep-related problems were responsible for their relapse.[19] A second study stated that of those who reported sleep problems, 11% used cannabis to compensate.[20] Finally, more detail was provided by Levin and colleagues[16] who reported that a median of 13.3% of a large sample of adult cannabis smokers relapsed to cannabis use after experiencing sleep problems including: "waking up during the night" (15.8% relapsed); "sleep less than usual" (15.6% relapsed); "trouble falling asleep" (14.6% relapsed); "waking up earlier than usual" (12.0% relapsed); "strange dreams" (10.2% relapsed); "sleep more than usual" (8.7% relapsed); "vivid dreams" (7.8% relapsed); and "other sleep problems" (33.3% relapsed).

A final article combined data from 5 studies to analyze the predictors of relapse (3 were published cannabis withdrawal medication trials[49,50,54] and 2 were unpublished studies on cannabis relapse). Data were limited to a combined total of 51 participants who had received placebo conditions in these cannabis withdrawal medication trials. Only tobacco smoking status (smokers were 19 times more likely to relapse to cannabis) and age of onset to cannabis use (all those who relapsed were aged over 25 years when they started smoking cannabis) were significant predictors of relapse. In contrast, the severity of relapse (number of self-administered cigarette puffs recorded by those who relapsed) was predicted by (1) increased ratings of feeling "high"; (2) objectively measured sleep onset latency (every 10 minutes increased the estimated number of puffs by 81%); and (3) increased ratings of feeling "miserable."

Conclusions

In our review of 36 articles that included a measure of cannabis withdrawal and sleep, the most striking finding was a general lack of studies that used validated or objective measures. Moreover, there was a lack of studies that controlled for confounding variables such as other substance or medication use and potentially common preexisting sleep-affecting conditions such as chronic pain and depression. Among other less common limitations, these faults resulted in our reporting that the relevant articles were of low to moderate quality. Across these articles, a withdrawal syndrome caused by abstaining from cannabis use was consistently reported. In contrast, the specifics of sleep-related symptoms of withdrawal remain somewhat unclear. Just over half of the participants across studies reported experiencing multiple symptoms of cannabis withdrawal when abstaining from cannabis use. For approximately one third of these individuals, these symptoms included a self-reported sleep-related problem, most commonly trouble falling asleep, waking up during the night, and/or experiencing strange dreams. Notably, during attempts at cannabis abstinence among participants of these studies on cannabis withdrawal, just over half reported relapsing to cannabis use and approximately 1 in 10 of these individuals report that this relapse was an attempt to alleviate problems sleeping.

Across studies that reported prevalence statistics, when abstaining from cannabis use, participants commonly reported experiencing "trouble sleeping" (41.5% of participants on average), "strange dreams" (34.4%), and "waking up early" (33.2%), whereas "sleeping more than usual" was less common (10.9%). In addition, participants commonly self-reported reductions in the total amount of time they spent asleep (this was observed in only half of the studies that objectively measured sleep time) and corresponding reductions to sleep efficiency and sleep quality. In contrast, the impact of these symptoms on the experience of sleep is uncertain. That is, reports of sleep satisfaction were largely unchanged, and findings from across studies using objective sleep measures (such as polysomnography) were mixed. However, there was a trend in line with the self-reported sleep "disturbance" in that periodic limb movements and waking after sleep onset may increase during withdrawal. In addition, sleep latency may increase and latency to REM sleep may decrease in withdrawal. As such, these indications of disturbed sleep should be of particular focus in future research.

While the specific mechanisms by which sleep is affected during cannabis withdrawal remain unclear without further study with consistency in sleep measures and timeframe, there is substantial support for the presence of disruption, although there was inconsistent evidence that this leads to relapse. Importantly, the health impact of sleep disruptions during cannabis withdrawal also remains to be assessed and is a necessary topic for future research among samples of cannabis abstainers. As sleep problems during cannabis withdrawal are common, to best prepare individuals seeking to abstain from cannabis use, it is important to assess and address any sleep problems as necessary during treatment. Given the risk of bias associated with the reviewed studies, there is a clear need for large-scale, longitudinal, and well-controlled studies on the specific effects of cannabis abstinence on sleep. It is particularly important for future study to address the impact of cannabis use history and dose on sleep-related withdrawal symptoms as well as their health impact and intensity timeline.

Author contributions

Peter Gates and Lucy Albertella were involved in the database searching, data extraction, and interpretation of results as well as writing the manuscript. Jan Copeland was involved with project design and supervision as well as providing comments and revisions to draft submissions.

References

[1] United Nations Office on Drugs and Crime. *World Drug Report 2013*. New York: United Nations Publication; 2013.

[2] Hall W, Degenhardt L. The adverse health effects of chronic cannabis use. *Drug Test Anal*. 2014;6:39–45.

[3] Budney AJ, Hughes JR. The cannabis withdrawal syndrome. *Curr Opin Psychiatry*. 2006;19:233–238.

[4] American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington: American Psychiatric Association; 1994.

[5] Wu LT, Woody GE, Yang C, Pan JJ, Reeve BB, Blazer DG. A dimensional approach to understanding severity estimates and risk correlates of marijuana abuse and dependence in adults. *Int J Methods Psychiatr Res*. 2012;21:117–133.

[6] Agrawal A, Pergadia ML, Lynskey MT. Is there evidence for symptoms of cannabis withdrawal in the national epidemiologic survey of alcohol and related conditions? *Am J Addict*. 2008;17:199–208.

[7] Compton WM, Saha TD, Conway KP, Grant BF. The role of cannabis use within a dimensional approach to cannabis use disorders. *Drug Alcohol Depend*. 2009;100:221–227.

[8] Gillespie NA, Neale MC, Prescott CA, Aggen SH, Kendler KS. Factor and item-response analysis DSM-IV criteria for abuse of and dependence on cannabis, cocaine, hallucinogens, sedatives, stimulants and opioids. *Addiction*. 2007;102:920–930.

[9] Hartman CA, Gelhorn H, Crowley TJ, et al. Item response theory analysis of DSM-IV cannabis abuse and dependence criteria in adolescents. *J Am Acad Child Adolesc Psychiatry*. 2008;47:165–173.

[10] Hasin DS, O'Brien CP, Auriacombe M, et al. DSM-5 criteria for substance use disorders: recommendations and rationale. *Am J Psychiatry*. 2013;170:834–851.

[11] Piontek D, Kraus L, Legleye S, Buhringer G. The validity of DSM-IV cannabis abuse and dependence criteria in adolescents and the value of additional cannabis use indicators. *Addiction*. 2011;106:1137–1145.

[12] Budney AJ. Are specific dependence criteria necessary for different substances: how can research on cannabis inform this issue? *Addiction*. 2006;101(Suppl 1):125–133.

[13] American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington: American Psychiatric Association; 2013.

[14] Allsop DJ, Norberg MM, Copeland J, Fu S, Budney AJ. The Cannabis Withdrawal Scale development: patterns and predictors of cannabis withdrawal and distress. *Drug Alcohol Depend*. 2011;119:123–129.

[15] Hasin DS, Keyes KM, Alderson D, Wang S, Aharonovich E, Grant BF. Cannabis withdrawal in the United States: results from NESARC. *J Clin Psychiatry*. 2008;69:1354–1363.

[16] Levin KH, Copersino ML, Heishman SJ, et al. Cannabis withdrawal symptoms in non-treatment-seeking adult cannabis smokers. *Drug Alcohol Depend*. 2010;111:120–127.

[17] Wiesbeck GA, Schuckit MA, Kalmijn JA, Tipp JE, Bucholz K, Smith TL. An evaluation of the history of a marijuana withdrawal syndrome in a large population. *Addiction*. 1996;91:1469–1478.

[18] Arendt M, Rosenberg R, Foldager L, Sher L, Munk-Jorgensen P. Withdrawal symptoms do not predict relapse among subjects treated for cannabis dependence. *Am J Addict*. 2007;16:461–467.

[19] Budney AJ, Vandrey RG, Hughes JR, Thostenson JD, Bursac Z. Comparison of cannabis and tobacco withdrawal: severity and contribution to relapse. *J Subst Abuse Treat*. 2008;35:362–368.

[20] Copersino ML, Boyd SJ, Tashkin DP, et al. Cannabis withdrawal among non-treatment-seeking adult cannabis users. *Am J Addict*. 2006;15:8–14.

[21] Cornelius JR, Chung T, Martin C, Wood DS, Clark DB. Cannabis withdrawal is common among treatment-seeking adolescents with cannabis dependence and major depression, and is associated with rapid relapse to dependence. *Addict Behav*. 2008;33:1500–1505.

[22] Dawes GM, Sitharthan T, Conigrave KM, Phung N, Weltman M. Patients admitted for inpatient cannabis detoxification: withdrawal symptoms and impacts of common comorbidities. *J Subst Use*. 2011;16:392–405.

[23] Ehlers CL, Gizer IR, Vieten C, et al. Cannabis dependence in the San Francisco family study: age of onset of use, DSM-IV symptoms, withdrawal, and heritability. *Addict Behav*. 2010;35:102–110.

[24] Winstock AR, Lea T, Copeland J. Lithium carbonate in the management of cannabis withdrawal in humans: an open-label study. *J Psychopharmacol*. 2009;23:84–93.

[25] Vandrey R, Budney A, Moore B, Hughes J. A cross-study comparison of cannabis and tobacco withdrawal. *Am J Addict*. 2005;14:54–63.

[26] Gates PJ, Albertella L, Copeland J. The effects of cannabinoid administration on sleep: a systematic review of human studies. *Sleep Med Rev*. 2014;18:477–487.

[27] Reinarman C, Nunberg H, Lanthier F, Heddleston T. Who are medical marijuana patients? Population characteristics from nine California assessment clinics. *J Psychoact Drugs*. 2011;43:128–135.

[28] Tringale R, Jensen C. Cannabis and insomnia. *Depression*. 2011;4:0–68.

[29] Schofield D, Tennant C, Nash L, et al. Reasons for cannabis use in psychosis. *Aust N Z J Psychiatry*. 2006;40:570–574.

[30] Glozier N, Martiniuk A, Patton G, et al. Short sleep duration in prevalent and persistent psychological distress in young adults: the DRIVE study. *Sleep*. 2010;33:1139–1145.

[31] Freeman D, Brugha T, Meltzer H, Jenkins R, Stahl D, Bebbington P. Persecutory ideation and insomnia: findings from the second British national survey of psychiatric morbidity. *J Psychiatr Res*. 2010;44:1021–1026.

[32] Wong MM, Brower KJ, Zucker RA. Childhood sleep problems, early onset of substance use and behavioral problems in adolescence. *Sleep Med*. 2009;10:787–796.

[33] Mednick SC, Christakis NA, Fowler JH. The spread of sleep loss influences drug use in adolescent social networks. *PLoS ONE*. 2010;5:e9775.

[34] Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Med*. 2009; 6(6): e1000097. doi:10.1371/journal.pmed1000097

[35] Vandrey R, Budney AJ, Kamon JL, Stanger C. Cannabis withdrawal in adolescent treatment seekers. *Drug Alcohol Depend*. 2005;78:205–210.

[36] Budney AJ, Moore BA, Vandrey RG, Hughes JR. The time course and significance of cannabis withdrawal. *J Abnorm Psychol*. 2003;112:393–402.

[37] Budney AJ, Novy PL, Hughes JR. Marijuana withdrawal among adults seeking treatment for marijuana dependence. *Addiction*. 1999;94:1311–1322.

[38] Haney M, Cooper ZD, Bedi G, Vosburg SK, Comer SD, Foltin RW. Nabilone decreases marijuana withdrawal and a laboratory measure of marijuana relapse. *Neuropsychopharmacology*. 2013;38:1557–1565.

[39] Vandrey R, Stitzer ML, Mintzer MZ, Huestis MA, Murray JA, Lee D. The dose effects of short-term dronabinol (oral THC) maintenance in daily cannabis users. *Drug Alcohol Depend*. 2013;128:64–70.

[40] Vandrey R, Smith M, McCann U, Budney A, Curran E. Sleep disturbance and the effects of extended-release zolpidem during cannabis withdrawal. *Drug Alcohol Depend*. 2011;117:38–44.

[41] Vandrey R, Budney A, Hughes J, Liguori A. A within-subject comparison of withdrawal symptoms during abstinence from cannabis, tobacco, and both substances. *Drug Alcohol Depend*. 2008;92:48–54.

[42] Pranikoff K, Karacan I, Larson EA, Williams RL, Thornby JI, Hursch CJ. Effects of marijuana smoking on the sleep EEG. Preliminary studies. *J Fla Med Assoc*. 1973;60:28–31.

[43] Penetar DM, Looby AR, Ryan ET, Maywalt MA, Lukas SE. Bupropion reduces some of the symptoms of marihuana withdrawal in chronic marihuana users: a pilot study. *J Subst Abuse Res Treat*. 2012;6:63–71.

[44] Milin R, Manion I, Dare G, Walker S. Prospective assessment of cannabis withdrawal in adolescents with cannabis dependence: a pilot study. *J Am Acad Child Adolesc*. 2008;47:174–179.

[45] McClure EA, Stitzer ML, Vandrey R. Characterizing smoking topography of cannabis in heavy users. *Psychopharmacology*. 2012;220:309–318.

[46] Mathers DC, Ghodse AH. Cannabis and psychotic illness. *Br J Psychiatry*. 1992;161:648–653.
[47] Jones RT, Benowitz N, Bachman J. Clinical studies of cannabis tolerance and dependence. *Ann N Y Acad Sci*. 1976;282:221–239.
[48] Haney M, Bedi G, Cooper ZD, et al. Predictors of marijuana relapse in the human laboratory: robust impact of tobacco cigarette smoking status. *Biol Psychiatry*. 2013;73:242–248.
[49] Haney M, Hart CL, Vosburg SK, et al. Effects of baclofen and mirtazapine on a laboratory model of marijuana withdrawal and relapse. *Psychopharmacology*. 2010;211:233–244.
[50] Haney M, Hart CL, Vosburg SK, Comer SD, Reed SC, Foltin RW. Effects of THC and lofexidine in a human laboratory model of marijuana withdrawal and relapse. *Psychopharmacology*. 2008;197:157–168.
[51] Haney M, Ward AS, Comer SD, Foltin RW, Fischman MW. Abstinence symptoms following oral THC administration to humans. *Psychopharmacology*. 1999;141:385–394.
[52] Haney M, Ward AS, Comer SD, Foltin RW, Fischman MW. Abstinence symptoms following smoked marijuana in humans. *Psychopharmacology*. 1999;141:395–404.
[53] Haney M, Ward AS, Comer SD, Hart CL, Foltin RW, Fischman MW. Bupropion SR worsens mood during marijuana withdrawal in humans. *Psychopharmacology*. 2001;155:171–179.
[54] Cooper ZD, Foltin RW, Hart CL, Vosburg SK, Comer SD, Haney M. A human laboratory study investigating the effects of quetiapine on marijuana withdrawal and relapse in daily marijuana smokers. *Addict Biol*. 2013;18:993–1002.
[55] Cohen-Zion M, Drummond SP, Padula CB, et al. Sleep architecture in adolescent marijuana and alcohol users during acute and extended abstinence. *Addict Behav*. 2009;34:976–979.
[56] Budney AJ, Hughes JR, Moore BA, Novy PL. Marijuana abstinence effects in marijuana smokers maintained in their home environment. *Arch Gen Psychiatry*. 2001;58:917–924.
[57] Bolla KI, Lesage SR, Gamaldo CE, et al. Sleep disturbance in heavy marijuana users. *Sleep*. 2008;31:901–908.
[58] Bolla KI, Lesage SR, Gamaldo CE, et al. Polysomnogram changes in marijuana users who report sleep disturbances during prior abstinence. *Sleep Med*. 2010;11:882–889.
[59] The Cochrane Collaboration. The Cochrane Collaboration's tool for assessing risk of bias. In: Higgins JPT, Green S, ed. *Cochrane Handbook for Systematic Reviews of Interventions*. Vol. 5.1.0. Oxford, UK: The Cochrane Collaboration; updated March 2011. Available at www.cochrane-handbook.org. Accessed January 29, 2014.
[60] The Cochrane Collaboration. Cochrane Effective Practice and Organisation of Care Review Group: Data collection checklist. The Cochrane Collaboration. Available at: http://epoc.cochrane.org/sites/epoc.cochrane.org/files/uploads/datacollectionchecklist.pdf. Published 2009. Accessed January 29, 2014.
[61] Viswanathan M, Ansari MT, Berkman ND, et al. Assessing the risk of bias of individual studies in systematic reviews of health care interventions. In: Agency for Healthcare Research and Quality, ed. *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*. AHRQ Publication No. 12-EHC047-EF. Rockville, MD: Agency for Healthcare Research and Quality; 2012.