CLINICAL REVIEW

Effect of illicit recreational drugs upon sleep: Cocaine, ecstasy and marijuana

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KEYWORDS
Cocaine;
Ecstasy;
Cannabis;
Marijuana;
Tetrahydrocannabinol;
Recreational drugs;
Sleep;
Withdrawal

Summary The illicit recreational drugs cocaine, ecstasy and marijuana have pronounced effects upon sleep. Administration of cocaine increases wakefulness and suppresses REM sleep. Acute cocaine withdrawal is often associated with sleep disturbances and unpleasant dreams. Studies have revealed that polysomnographically assessed sleep parameters deteriorate even further during sustained abstinence, although patients report that sleep quality remains unchanged or improves. This deterioration of objective sleep measures is associated with a worsening in sleep-related cognitive performance. Like cocaine, 3,4-methylenedioxymethamphetamine (MDMA; "ecstasy") is a substance with arousing properties. Heavy MDMA consumption is often associated with persistent sleep disturbances. Polysomnography (PSG) studies have demonstrated altered sleep architecture in abstinent heavy MDMA users. Smoked marijuana and oral Δ-9-tetrahydrocannabinol (THC) reduce REM sleep. Moreover, acute administration of cannabis appears to facilitate falling asleep and to increase Stage 4 sleep. Difficulty sleeping and strange dreams are among the most consistently reported symptoms of acute and subacute cannabis withdrawal. Longer sleep onset latency, reduced slow wave sleep and a REM rebound can be observed. Prospective studies are needed in order to verify whether sleep disturbances during cocaine and cannabis withdrawal predict treatment outcome.
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Introduction

"Recreational drug use" is a term for a substance use pattern that has become highly prevalent. Recreational drug users are generally well-integrated and may belong to any social class. They usually resort to illegal drugs at weekend parties, in order to reduce stress and to escape from the daily routine. Also, the substances are welcome for their socializing properties, and some of them for their enhancement of dancing capabilities.

This review considers the illicit recreational drugs cocaine, ecstasy and marijuana. Further examples of substances used in the described manner are amphetamine, methamphetamine, LSD, psilocybin mushrooms, ketamine and gamma-hydroxybutyrate. Many of these drugs, in particular cocaine, are clearly not restricted to a recreational pattern of use.

It is estimated that 42% of US American adolescents have experience with marijuana before the end of secondary school, 9% with cocaine and 7% with ecstasy.[1] An estimated 4.2 million Americans are classified with current dependence on or abuse of marijuana, and almost 1.7 million with dependence on or abuse of cocaine.[2] These numbers are higher than the corresponding figures for prescription-type pain relievers used nonmedically (1.6 million), prescription-type tranquilizers (400,000) and heroin (300,000).[2]

We carried out a search in the electronic databases Medline (since 1966), Embase, PsycINFO, Psyndex and the Cumulative Index to Nursing and Allied Health Literature (CINAHL). The key words included "cocaine", "3,4-methylenedioxymethamphetamine", "MDMA" and "ecstasy" as well as "cannabis", "marijuana", "tetrahydrocannabinol" and "THC". These terms were entered into the databases in conjunction with the term "sleep". Articles published until August 2007 were eligible, and reference lists of relevant articles were screened for further related studies.

Cocaine

Acute cocaine administration

The competitive inhibition of presynaptic dopamine transporters in the nucleus accumbens and prefrontal cortex, leading to an increase in dopamine availability, has been proposed to constitute the primary neurophysiologic equivalent of central cocaine effects.[3] Acute subjective effects of cocaine intake are euphoria, orgiastic feelings, restlessness, motor activation and increased alertness.

Trouble sleeping is a frequently cited adverse effect of cocaine intake.[4,5] Polysomnography (PSG) studies have confirmed the stimulant properties of cocaine, demonstrating longer sleep latency, reduced total sleep time and suppression of REM sleep after acute cocaine administration.[6-8] Acute effects of cocaine upon sleep resemble those of other psychostimulants such as amphetamine.[9]

Cocaine withdrawal

During acute withdrawal, cocaine-dependent individuals often experience depressed mood, psychomotor agitation or retardation, increased appetite, fatigue, sleep disturbances and unpleasant dreams.[10,11]

To date, eight PSG studies[7,8,12-17] of cocaine withdrawal have been published, mostly non-randomized controlled trials (see Table 1). Three studies administered cocaine in simulated binges during the inpatient phase.[8,16,17] Results were similar to the studies with previous binges in the patients' natural environment.[12-15] It has been shown that during acute cocaine withdrawal, total sleep time is significantly reduced,[8,12-17] approximating that of untreated chronic insomniacs.[21] Sleep onset latency is prolonged and sleep efficiency is decreased.[8,12-18] An increase in REM sleep percentage and reduced REM latency are observed.[7,8,12-16] These changes in REM sleep are consistent with the subjective withdrawal symptom of increased dreaming.[10,11] It has been found that smaller doses of cocaine administered in the morning may improve sleep in cocaine-dependent subjects, probably by attenuating withdrawal effects.[19]

During the subacute phase of cocaine withdrawal, commonly defined as starting on day 10, PSG parameters of sleep continuity deteriorate even further. Total sleep time decreases,[12-14,16,17] and sleep latency and sleep efficiency also change in the direction of even poorer sleep.[12-14,16,17] REM latency remains significantly reduced.[12,14,16]

It has been shown that cognitive performance deteriorates during subacute cocaine withdrawal.[17,20] Reaction time on a vigilance task increases,[17,20] which is considered to be a sensitive measure of growing sleep pressure in the context of sleep deprivation.[21] Also, the sleep-dependent performance on a motor sequence task is compromised and correlates with an individual's total sleep during withdrawal.[17]

These findings are most notable in view of the fact that subjective sleep quality remains unchanged or improves during subacute withdrawal.[12,16,17,22,23] This phenomenon is the exact opposite of the

Table 1 PSG studies investigating sleep during cocaine withdrawal

Authors	Subjects (no.)	Intervention	Method	Major findings
Watson et al.[7]	3 light cocaine users	1 drug night, 3 d recovery	PSG	Drug night: ↓ REM sleep. Recovery: REM rebound
Kowatch et al.[12]	3 cocaine-dependent	17 d abstinence	PSG, subjective reports	↑ Wakefulness, ↓ SE, ↓ SWS, REM rebound, subjective: about same as usual
Gillin et al.[13]	6 stimulant abusers	Placebo arm of lisuride treatment trial, 18 d abstinence	PSG	↑ SOL, ↓ TST, ↓ SWS, REM rebound
Thompson et al.[14]	7 stimulant abusers	14 d abstinence	PSG	Acute withdrawal: REM rebound, subacute withdrawal: ↓ TST
Lukas et al.[15]	20 cocaine- and heroin-dependent	9 d abstinence before buprenorphine treatment	PSG	↑ SOL, ↓ TST, ↓ SE, ↓ SWS, REM rebound
Johanson et al.[8]	3 cocaine-dependent	8–10 d abstinence, 5 d of 600 mg cocaine, 15–16 d abstinence	PSG, MSLT	Cocaine use: ↑ SOL, ↓ SE, ↓ REM sleep. Withdrawal: ↑ SOL, ↓ SE, ↓ REM latency, MSLT: ↑ SOL during subacute withdrawal
Pace-Schott et al.[16]	5 cocaine-dependent	3 d abstinence, 3 d of 600 mg crack, 15 d abstinence	PSG, subjective reports, cognitive tasks	↑ SOL, ↓ SE, ↓ REM latency across binge-abstinence, subjective: slight improvement, deterioration of cognitive performance
Morgan et al.[17]	12 cocaine-dependent	3 d abstinence, 3 d of 223 mg cocaine, 17 d abstinence	PSG, spectral power, subjective reports, cognitive tasks	↑ SOL, ↓ TST, ↓ SE across binge-abstinence, ↑ δ spectral power during subacute withdrawal, subjective: improvement, deterioration of cognitive performance

Abbreviations: d, days; MSLT, multiple sleep latency test; PSG, polysomnography; SE, sleep efficiency; SOL, sleep onset latency; SWS, slow wave sleep; TST, total sleep time.

distorted sleep perception in primary insomniacs, who typically underestimate their sleep quality. It has not been studied why cocaine-dependent subjects do not recognize this deterioration of sleep during subacute withdrawal. A possible explanation is that, although slow wave sleep (SWS) percentage is low both during acute and subacute withdrawal,[12–14,17] δ spectral power may increase during subacute withdrawal.[17] An increased δ spectral power is associated with better self-reports of sleep quality.[24]

Ecstasy

Acute and subacute ecstasy effects

3,4-Methylenedioxymethamphetamine (MDMA; "ecstasy") is a drug that is frequently used by visitors of raves or techno parties in large dance clubs. MDMA induces rapid release of serotonin via interaction with presynaptic serotonin uptake carriers.[25] MDMA also induces rapid dopamine release and binds to a variety of neurotransmitter receptors, especially serotonin 5-HT$_2$ receptors.[25] MDMA effects such as feelings of closeness to others, increased empathy and self-perception are summarized as the "entactogenic" properties of this agent ("entactogen" from Greek and Latin, "producing a touching within"). Furthermore, ingestion of ecstasy is associated with cognitive and perceptual changes that resemble effects of psychedelics and with amphetamine-like hyperactivity and increased energy.

MDMA users commonly report restless, disturbed sleep during the 48 h following MDMA intake.[26,27] 3,4-Methylenedioxy-N-ethylamphetamine (MDE; "eve") has similar effects as MDMA. The only PSG investigation on acute effects of entactogens was conducted with MDE. It showed an increase in

wakefulness and an almost complete suppression of REM sleep.[28]

Persistent effects of heavy ecstasy use

A number of studies have indicated that heavy MDMA use is associated with persistent neuropsychiatric symptoms such as, most notably, impaired episodic memory and learning performance,[29] but also anxiety, depersonalization, depression, and sleep disturbances.[26,30–32] Interpretation of these studies is complicated owing to methodological difficulties such as polydrug usage and the possibility of pre-existing differences.

There is conflicting evidence with respect to the PSG patterns in abstaining heavy MDMA users. A recent study[33] replicated earlier findings[34] that Stage 2 sleep is reduced in these individuals. Furthermore, Stage 1 sleep is increased and total sleep time is reduced, although findings were only near-significant in one study and significant in the other. There was a trend for reduced REM latency.[33] No significant correlations were detected between previous marijuana use and Stage 2 or Stage 1 sleep.[33] In a third PSG study of abstinent MDMA users, Stage 2 sleep was decreased without achieving statistical significance.[35] Furthermore, this study indicated that sleep efficiency and SWS are increased in ecstasy users.[35] However, these latter findings need to be viewed cautiously since control subjects had remarkably low sleep efficiency and decreased SWS.[35]

Cannabis

Acute and chronic cannabis administration

The cannabis plant contains over 60 cannabinoids. Δ-9-Tetrahydrocannabinol (THC) is the constituent that is mainly responsible for the psychotropic effects of marijuana.[36] These psychotropic effects are mediated mostly by cannabinoid CB_1-receptors, which can be found in high concentrations in the frontal cortex, cerebellum and basal ganglia.[37] CB_1-receptors activate a variety of signal transduction pathways and interact with numerous neurotransmitters and neuromodulators. Acute subjective marijuana effects are highly variable, and contradictory effects may be observed depending on individual and condition. Often, marijuana induces mild euphoria, talkativeness, intensification of sensory experiences, difficulty concentrating, altered time perception, relaxation and drowsiness.

Interpretation of the available PSG studies of cannabis effects is difficult due to a number of methodological limitations. Sample sizes were often small, and most studies were carried out in the 1970s. There is considerable heterogeneity with respect to administered dosage, time and route of administration, specificity for THC, and, notably, the extent of previous drug consumption, possibly leading to withdrawal effects during baseline or to tolerance. Several studies have shown that acute administration of THC decreases sleep latency,[38] and is associated with reports of greater ease in getting to sleep.[39,40] Yet, arousing effects may predominate initially, and in a few studies with high THC doses or marijuana-naive subjects, findings were more suggestive of increments in sleep onset latency.[41–43] There is some evidence indicating that cannabis reduces Stage 3, but increases Stage 4 and total slow wave sleep,[45–47] but contradictory effects have also been observed.[41] Furthermore, it has been found consistently that THC decreases total REM sleep and REM density.[41,46,48–51] Owing to the slow elimination of THC and its active metabolites, sedative effects are sometimes still present the following morning.[38,47] The combination of THC with cannabidiol, an important non-psychoactive ingredient of marijuana, leads to an increase in wakefulness compared to THC alone.[47]

PSG studies of chronic marijuana administration have suggested that some tolerance occurs to the sleep-inducing[52,53] and SWS-enhancing[45,51,52] effects of cannabis. Tolerance to REM sleep effects may be less pronounced,[46] but evidence is conflicting.[48,53] A study of subjective changes of marijuana effects over the years indicated that desirable effects of marijuana upon sleep are reported less frequently after years of use compared to initial ratings.[54]

Table 2 gives an overview over studies investigating the effects of cannabis upon objective sleep measures.

Cannabis withdrawal

Anger and irritability, anxiety and nervousness, restlessness, weight loss, sleep difficulty and strange dreams are frequently reported marijuana withdrawal effects.[55–57] Less common symptoms are depressed mood, chills, shakiness, stomach pain and sweating.[55] Cannabis withdrawal resembles nicotine withdrawal with respect to symptom profile, magnitude and time course.[58,59]

There is quite a substantial number of recent studies on subjective sleep measures during cannabis withdrawal.[55] Difficulty in sleeping and strange dreams have been reported with high cross-study reliability.[55] They generally occur within 24–72 h of discontinuation of cannabis use

Table 2 Studies investigating the effect of smoked marijuana and oral THC upon sleep

Study	Subjects (no.)	Intervention	Major findings
Gillin et al.[42]	3 psychiatric pts	40 mg THC	↓ REM sleep
Kales et al.[47]	4 naive, 4 chronic users	Smoked marijuana	↓ REM sleep. Recovery: REM rebound
Freemon[48]	2	20 mg THC	↓ REM %. Recovery: ↑ wakefulness, ↓ REM latency
Pivik et al.[65]	6	<20 mg THC	↓ WASO. Recovery: ↓ Stage 1, ↓ REM latency
Cousens and DiMascio[38]	9 insomniacs	10—30 mg THC	↓ Sleep onset latency
Bobon et al.[43]	1 psychiatric pt	20 mg Δ-8-THC	↑ Wakefulness, ↑ REM latency
Hosko et al.[44]	7 (2 naive, 1 heavy user)	20 mg THC	No consistent alterations
Pranikoff et al.[52]	30 chronic users	Smoked marijuana until "high"	↑ Stage 2, ↓ Stage 4 compared to abstinent users
Barratt et al.[45]	12	2 marijuana cigarettes (1.6% THC)	Acute: ↑ SWS, chronic administration: ↓ SWS. Withdrawal: ↓ SWS
Feinberg et al.[46]	7 chronic users	70—210 mg THC	↑ Stage 4, ↓ REM density, ↓ REM sleep. Withdrawal: ↑ SOL, ↓ SWS, REM rebound
Tassinari et al.[41]	8 (7 naive)	70 mg THC	↑ Stage 2, ↓ REM sleep
Feinberg et al.[50]	4 chronic users	Marijuana extract (70—210 mg THC)	Low dosage: ↑ Stage 4, ↓ REM density. Withdrawal: ↑ SOL
Karacan et al.[53]	32 chronic users	Usual pattern of marijuana use	↑ REM %, ↑ SOL
Freemon[51]	2	30 mg THC	Chronic administration: ↓ SWS. Withdrawal: ↑ wakefulness, ↓ SWS
Nicholson et al.[47]	8	15 mg THC, 5 mg THC+CBD, 15 mg THC+CBD	15 mg THC: ↑ sleepiness next morning. 15 mg THC+CBD: ↑ wakefulness, ↓ Stage 3, ↑ sleepiness next morning
Walther et al.[89]	6 pts with dementia and nighttime agitation	2.5 mg THC	↓ Nocturnal motor activity

Abbreviations: CBD, cannabidiol; MSLT, multiple sleep latency test; PSG, polysomnography; pts, patients; SOL, sleep onset latency; SWS, slow wave sleep; THC: Δ-9-tetrahydrocannabinol; TST, total sleep time; WASO, wakefulness after sleep onset.

and persist for 6—7 weeks.[57,60] Resumption of cannabis use attenuates sleep disturbances.[61—63] Treatment of cannabis withdrawal symptoms by means of oral substitution of THC improves sleep or even reinstitutes subjectively normal sleep.[40,64]

The available PSG studies of cannabis withdrawal were designed as non-randomized, controlled trials. They have demonstrated increments in sleep onset latency and wakefulness after sleep onset.[46,49—51] Total SWS is reduced[45,46,51] and REM sleep is increased[46,48,49,65]. This increase in REM sleep is consistent with the subjective abstinence symptom of "strange dreams".[55,56]

Outlook

Every year, a combined 2.2 million Americans receive treatment for cocaine or cannabis abuse in specialized facilities, compared to 2.5 million alcoholics receiving specialized treatment.[2]

Treatment of cocaine and cannabis dependence is difficult and expensive.[66,67] More research on potential pharmacotherapies is warranted.

It can be hypothesized that the poor sleep quality during cocaine withdrawal has detrimental effects upon treatment outcome. The demonstrated impairments of vigilance and learning performance may put cocaine users at increased risk of relapse. On the other hand, it has been shown that the severity of withdrawal symptoms including sleep disturbances predicts poor treatment outcome in cocaine dependence.[68] Similarly, it has been suggested that in cannabis dependence, sleep problems and other withdrawal symptoms make cessation more difficult and that resumption of cannabis use serves as a negative reinforcer.[57,69,70] There is need for prospective studies to verify whether sleep disturbances during cocaine and cannabis withdrawal are predictive of relapse. Such a relationship would not only provide a prognostic tool, but it might also open new

perspectives on therapeutic strategies. In alcohol addiction, the predictive value of sleep disturbances for relapse has been established,[71–73] and successful treatment options have been derived from this observation.[74]

Substances recently tested as pharmacotherapy for cocaine abuse interact directly with sleep–wake mechanisms. The effectiveness of substances with gamma amino butyric acid (GABA)-mediated sedative properties such as baclofen has been demonstrated.[75–77] Modafinil acts in the opposite direction, and constitutes another promising candidate for treatment of cocaine dependence.[78,79] It is a stimulant substance that may be able to restore cognitive functioning in cocaine withdrawal, as it does in sleep-deprived individuals when given in the morning.[80] The question of whether modafinil possesses abuse potential is discussed controversially at present.[81,82] There is need for randomized controlled trials that examine the effect of GABA-medications and stimulants such as modafinil upon objective sleep measures, cognitive performance as well as treatment outcome. This would shed more light upon the clinical relevance of the impairments of sleep-dependent cognitive performance.

Agonist replacement therapy has become a well-established approach to treat opiate and nicotine dependence. Preliminary findings of substitution therapy for cannabis dependence are promising,[40,64] demonstrating an attenuation of withdrawal symptoms including sleep disturbances. Randomized controlled trials on the effect of THC substitution upon treatment outcome are under way.

The question of whether MDMA induces serotonin neurotoxicity in humans has become a field of extensive research.[29] Since PSG is a highly sensitive instrument to detect subtle neurophysiologic alterations, it might prove to be particularly useful in this matter.

Individuals who are exposed to experimental depletion of the serotonin precursor tryptophan develop acute serotonin deficiency. PSG studies of tryptophan depletion have been carried out in healthy individuals[83–86] and in psychiatric patients.[85–88] The bottom line of these studies is that tryptophan depletion is associated with an increase in wakefulness and Stage 1 sleep and with a reduction in Stage 2 sleep. Phasic activity of REM sleep is enhanced.

These PSG patterns are in agreement with the sleep architecture observed in abstinent heavy MDMA users.[33,34] Prospective PSG studies are needed in order to investigate preexisting differences in sleep architecture between consequent MDMA users and non-user controls. Such prospective studies would also be capable of determining to what extent restitution occurs with prolonged abstinence. To this end, ecstasy users and controls would need to be followed up over a period of several years. Furthermore, it should be determined whether PSG abnormalities correlate with other presumed evidence of MDMA neurotoxicity such as PET examinations using serotonin transporter ligands.[29]

There is evidence that the sedative properties of marijuana may be of use in clinical practice. An open pilot study demonstrated the effectiveness and tolerability of THC for the treatment of agitated behavior at night in patients with severe dementia.[89] Nocturnal motor activity was reduced by 59% from baseline, as evidenced by wrist actigraphy. Other parameters such as appetite disturbances and irritability improved as well. No adverse effects were observed after single and repeated administrations of THC. A systematic review found that atypical antipsychotics often fail to reduce behavioral symptoms of dementia[90] Adverse effects occur frequently.[90] For safety concerns, co-administration of benzodiazepines is not recommended.[91] The limitations of the available treatment options warrant the search for effective and well-tolerated alternatives. Randomized controlled trials with large sample sizes and longer treatment periods are needed in order to corroborate the preliminary findings for THC.

Cannabis-based medicines have also been shown to improve subjective sleep quality in patients with chronic pain syndromes, such as multiple sclerosis, peripheral neuropathy, rheumatoid arthritis and cancer pain.[92] To a great extent, this improvement may be due to analgesic, anti-inflammatory and spasmolytic effects[36] resulting in nocturnal symptom relief, in addition to the hypnotic properties of cannabis.

Practice points

1. Consider and routinely investigate the possibility that complaints of sleep disturbances may be related to use of illicit drugs, especially in younger patients.
2. In cocaine- or cannabis-dependent individuals, sleep disturbances including unpleasant dreams constitute important withdrawal symptoms and their treatment needs to be incorporated into the overall treatment plan.

3. Even if subjective assessments suggest normal or only slightly disturbed sleep during subacute cocaine withdrawal, PSG parameters may reveal considerable sleep disturbance. This sleep disturbance contributes to a deterioration of cognitive performance.

Research agenda

1. Prospective studies on the predictive value of sleep disturbances during cocaine and cannabis withdrawal for long-term outcome.
2. Randomized controlled trials of cocaine withdrawal investigating the effect of GABA-medications and stimulant substances (e.g. modafinil) upon objective sleep measures, cognitive performance and treatment outcome.
3. Prospective PSG studies of ecstasy use, in order to investigate preexisting differences in sleep patterns and to detect to what extent restitution occurs with continued abstinence.
4. Randomized controlled trials of THC for treatment of selected types of sleep disturbances such as circadian rhythm disturbances in patients with dementia.

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