

## REVIEW

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# Sleep abnormalities associated with alcohol, cannabis, cocaine, and opiate use: a comprehensive review

Gustavo A. Angarita, Nazli Emadi, Sarah Hodges and Peter T. Morgan\*

## Abstract

Sleep abnormalities are associated with acute and chronic use of addictive substances. Although sleep complaints associated with use and abstinence from addictive substances are widely recognized, familiarity with the underlying sleep abnormalities is often lacking, despite evidence that these sleep abnormalities may be recalcitrant and impede good outcomes. Substantial research has now characterized the abnormalities associated with acute and chronic use of alcohol, cannabis, cocaine, and opiates. This review summarizes this research and discusses the clinical implications of sleep abnormalities in the treatment of substance use disorders.

**Keywords:** Sleep, Insomnia, Alcohol, Cannabis, Cocaine, Opiates

## Background

Sleep problems are commonly associated with drug and alcohol use. Nearly 70 % of patients admitted for detoxification report sleep problems prior to admission, and 80 % of those who report sleep problems relate them to their substance use [169]. The association between substance use and sleep problems appears to be bidirectional [105, 110], with sleep problems increasing risk for developing substance use disorders [31, 89, 210], and acute and chronic substance use leading to acute and chronic problems with sleep [44, 47, 89, 97, 104, 138, 156, 168]. Evidence also indicates that long-term abstinence from chronic substance use can reverse some sleep problems [13, 37]. This paper aims to explore and clarify the strong yet not entirely understood connection between abnormalities in sleep and substance use. By improving our understanding of sleep disorders that either predispose to substance use or are the result of chronic substance use, we may be better able to prevent and treat substance use disorders.

Understanding the sleep problems related to substance use disorders requires characterizing them both

subjectively and objectively, while considering how sleep responds to periods of use and abstinence. This review will describe such research with regard to alcohol, cannabis, cocaine, and opioids. In addition, this review will discuss evidence that sleep abnormalities predict use and relapse, and that sleep abnormalities can be modulated to improve clinical outcome. This paper will also review potential pharmacological agents that modulate sleep. Psychotherapy options, albeit evidence-based and of clear clinical value, will not be discussed in this review as these are addressed elsewhere [15, 110].

## Methods

This is a narrative, non-systematic review of clinical trials conducted in humans. For the literature search, Pubmed, Ovid Medline, and Web of Science databases were used. For each drug (e.g., alcohol, cannabis/marijuana, cocaine, and opioids/heroin) keywords included terms describing abnormal/pathological use (e.g., alcohol use disorders, alcohol abuse, alcohol dependence, and alcohol addiction, etc.) combined with terms referring to sleep or sleep abnormalities [e.g., sleep, insomnia, polysomnography, total sleep time, slow-wave sleep, rapid eye movement (REM) sleep, sleep latency, REM latency; these terms are defined in Table 1]. In addition to extracting data available in each of the retrieved articles, reference lists from

\*Correspondence: [peter.morgan@yale.edu](mailto:peter.morgan@yale.edu)  
Yale University Department of Psychiatry, Connecticut Mental Health Center, 34 Park Street, New Haven, CT 06519, USA

**Table 1 Sleep terminology**

Homeostatic sleep drive	The drive to sleep that progressively builds with continued wakefulness
Insomnia	A sleep disorder in which the quantity or quality of sleep is less than desired, usually characterized by difficulty falling or staying asleep, or waking too early, and experiencing daytime consequences of reduced sleep
Polysomnography (PSG)	A technique that records brain activity, eye movements, and muscle tone in order to study sleep and diagnose sleep disorders
Rapid eye movement (REM) sleep	The phase of sleep characterized by conjugate eye movements, paralysis of other muscles, and brain activity that is most similar to wakefulness
REM density	The frequency of rapid eye movements occurring during REM sleep. REM density increases over the course of the sleep period and is greatest when homeostatic sleep drive (sleep pressure) is lowest
REM latency	The amount of time from the onset of sleep to the onset of REM sleep
REM rebound	The characteristic increase in REM sleep after REM sleep deprivation
Self-administration	A method involving research participants administering a substance to themselves under observation in a clinical setting
Sleep architecture	The structure of sleep, including non-REM (stages N1, N2, and N3) and REM (stage R) sleep
Sleep efficiency (SE)	The percent of time in bed spent sleeping, calculated as total sleep time divided by time in bed
Sleep fragmentation	Disruption in sleep characterized by awakenings and transitions to light (stage N1) sleep from deeper sleep
Sleep latency (SL)	The amount of time from lights out to sleep onset
Slow-wave sleep (SWS)	Also known as stage N3 sleep, slow wave sleep is characterized by low frequency and high amplitude waves
Total sleep time (TST)	The amount of sleep in one complete episode of sleeping, usually reported in minutes
Wake after sleep onset (WASO)	The amount of time awake after the onset of sleep and before final waking

each retrieved article were examined to identify articles missed by the initial search. For each drug, the available literature on subjective measurements, objective measurements, the relationship between subjective and objective measurements, clinical and laboratory correlates of sleep outcomes, and pharmacotherapies related to sleep were summarized.

## Alcohol

### Subjective measurements

Alcohol is widely used as a sleep-promoting agent. However, as the consumption of alcohol becomes chronic, alcohol has less of an hypnotic effect [196]. Significant, self-reported sleep problems are highly prevalent among alcohol users with rates of clinical insomnia between approximately 35 and 70 % depending on the setting and stage of use, among other parameters [35, 48]. These rates are substantially higher than those observed in the general population (i.e. ~15 to 30 %) [32]. Complaints typically include difficulty falling asleep, frequent awakenings, daytime sleepiness, and abnormal sleep quality [15, 34, 196], but could also include hypersomnia [196]. Notably, sleep complaints associated with alcohol use disorders are one of the most refractory problems to resolve [34, 69, 82], and insomnia is the most frequent complaint among alcoholics after they stop drinking [132].

### Objective measurements

Objective measurement of sleep in persons with alcohol use disorders confirms self-reported sleep problems in

many respects, and provides additional insight into the nature of the underlying sleep abnormalities.

### Sleep latency (SL)

Although it is known that alcohol can decrease sleep latency when consumed by healthy persons [124], chronic use leads to increased sleep latency, consistent with individual self-report. Published studies show that SL is prolonged during periods of drinking [9, 33, 85, 199, 221], during acute withdrawal (e.g., weeks 1 and 2 of abstinence) [9, 33, 85, 199, 221], and during post-acute withdrawal (e.g., weeks 2 through 8) [33], (Table 2) with evidence for sleep latency prolongation in inpatient and outpatient settings (e.g., [83, 123, 183]), and when controlled for age and sex, among other variables [26]. After the second month of abstinence, sleep latency may still be increased [213], or normalized [174], with evidence for normalization also present after five [69] and 9 months of abstinence [213].

### Total sleep time (TST)

Congruent with increased sleep latency, total sleep time is reduced in persons with alcohol use disorders during periods of drinking, acute withdrawal, and post-acute withdrawal [33, 85, 86, 199, 221], with very few exceptions [9]. Numerous studies examining total sleep time from 2 to 4 weeks of abstinence document reduced sleep time compared to healthy controls [69, 83, 183] (Table 2). Reduced total sleep time has also been observed in study

**Table 2 Objective sleep changes during early and late abstinence, in comparison to healthy sleepers**

	Alcohol		Cocaine		Cannabis		Opioids	
	Early Abs	Late Abs	Early Abs	Late Abs	Early Abs	Late Abs	Early Abs	Late Abs
Sleep latency	?	↑	?	↑	↑	?	↑	↑
Total sleep time	?	↓	?	↓	↓	↓	↓	↓
Slow wave sleep	?	↓	↓	↓	↓	?	↓	↓
REM sleep	?	?	?	↓	↑	↓	↓	?
REM latency	?	?	↓	?	↓	?	↑	?

*Early Abs* Early Abstinence or acute withdrawal

*Late Abs* Late Abstinence or subacute withdrawal

? Insufficient data or conflicting results across studies

designs that control for age and sex, among other variables [26].

Total sleep time in persons with alcohol use disorder may improve after sustained abstinence. For instance, one group found decreased yet gradually improving TST among alcoholic subjects after 19 weeks, 14, and 27 months of abstinence (312, 335, and 349 min, respectively) [69]. Another study examined TST after 1–2 years of abstinence and found no abnormalities among subjects recruited from Alcoholics Anonymous vis-à-vis controls [2].

**Slow-wave sleep (SWS)**

Considerable evidence points to deficits in slow wave sleep time (i.e. stage 3 and stage 4 sleep, or stage N3 sleep in the newer nomenclature) or slow-wave sleep activity (i.e. EEG spectral power in the slow wave frequency range) in persons with alcohol use disorders [33]. Most of this evidence comes from studies reporting results from the first few weeks of abstinence, including acute withdrawal [196], subacute withdrawal (i.e. days 8 and 12); [106] (Table 2), and beyond [26, 69, 83, 127].

Although there is evidence that SWS deficits are recovered with prolonged abstinence, current literature does not provide a definitive time frame for these improvements, yet does suggest that it may be between 3 and 14 months [33] or longer. While one study found no difference between alcohol users and controls at 25 days abstinent [183], other studies found that SWS had improved at 3 months, and normalized at 9 months of abstinence [196]. In contrast, other studies have reported persistent deficits [69] or a trend toward deficits [2] after as long as 1–2 years of abstinence, with complete recovery occurring only after 1–4 years of abstinence [199].

Intriguingly, acute alcohol use has been shown to reverse the chronic slow wave sleep deficits observed in chronic alcohol users [33, 86]. Given the widespread importance of slow-wave sleep [65] in factors including

sleep continuity, learning, and memory, as well as other types of cognitive performance, the deficits associated with chronic use (and their reversal with acute use of alcohol) suggests the particular importance of slow-wave sleep in alcohol use disorders. More specifically, as the brain processes that underlie the generation of these slow waves appear to be chronically altered by chronic alcohol use, and to be temporarily restored by acute use, this chronic alteration is implicated as a potential factor in relapse.

**Rapid eye movement (REM)**

For both persons without alcohol use disorders (AUD) [118, 219] and individuals with alcohol use disorders, drinking alcohol acutely suppresses REM sleep time. For persons with AUD, REM rebound occurs several days later [33]. An early study of sleep in persons with AUD who were exposed to alcohol found that REM sleep, measured as a percentage of total sleep time (REM%) was less, relative to baseline, after 2–3 days of abstinence, but then rebounded after 5–6 days of abstinence [7]. This rebound in REM sleep has been explained as reflecting both an increased number of REM periods as well as shorter intervals between each REM cycle [196]. REM rebound has been documented after 2–3 weeks of abstinence [26, 69, 83, 127], and even after 27 months of abstinence [69].

Notwithstanding the above findings, the literature on alcohol and REM sleep has some inconsistencies (Table 2). For example, a meta-analysis examined six studies that did not consider covariates and four studies that controlled for variables such as age and sex (all participants abstinent for at least 3 weeks). Even though the analyses among all subjects showed no differences in REM measured as the percentage of total sleep (REM%), the analyses did find increased REM% in persons with AUD compared to controls when controlling for some variables [26]. Other studies have found

no difference in REM% between chronic alcohol users and normal controls in the second [106] and third [83] week of abstinence. Additionally, supporting the finding of no difference in REM between chronic alcohol users and controls, a study examining REM time after 4 weeks of abstinence found no difference between subjects with AUD and normal controls [183]. Another discrepancy appears in the form of a study that found REM% among participants with AUD to be reduced after 12 weeks of abstinence in comparison with REM% after 4 weeks of abstinence, arguing against a lasting REM rebound [171].

Possibly contributing to differences in REM sleep findings are variations across studies in how control participants were recruited [183] and how well these control subjects matched the subjects with AUD in terms of measures relevant to sleep architecture such as age. An example of this is a meta-analysis exhibiting different results depending on whether authors controlled for those variables or not [26]. Another factor could be that several studies report REM%, thus, the numbers are also a reflection of not one, but two sleep architecture measurements (e.g., REM and TST) that are both undergoing dynamic changes as subjects with AUD progress in abstinence [69].

#### **REM latency**

Data on REM latency in persons with alcohol use disorders is more limited but also show some discrepancies. For instance, while some studies report that REM latency is decreased during the second week of abstinence [69, 106], as well as up to two years later [69], other studies do not report differences in REM latency [26, 32] (Table 2). One potential explanation for the inconsistencies in this measure could lie in the heterogeneity of subjects with AUD with regard to co-occurring conditions like depression. Supporting this idea is the finding that AUD subjects with secondary depression exhibit shorter REM latency compared to AUD subjects who do not have secondary depression [83].

#### **Objective sleep quality or consolidation of sleep**

Several studies examining sleep in persons with alcohol use disorders also reported data on fragmentation of sleep. Sleep fragmentation reflects awakenings or switching from a deeper to a lighter stage of sleep, and is measured by the number of switches from one stage of sleep to another, the number of awakenings, and the time spent awake after sleep onset. The measurements of sleep fragmentation provide some insight into the objective quality of sleep. Results from these studies show consistent deficiencies in objective sleep quality, with an increase in sleep stage switches compared to healthy controls from day 2 of abstinence to as far out as 1–2 years of abstinence [2, 106, 196].

Sleep stage switches, number of awakenings and time awake after sleep onset were also found to be increased on the second night of abstinence compared to the second week of abstinence, which suggests greater abnormalities in objective sleep quality occur during the withdrawal period [106]. In addition, increased sleep fragmentation was observed after 3 and 9 months of abstinence [196].

#### **Relationship between subjective and objective outcomes**

Although there is limited published data on the relationship between subjective and objective sleep measurement in persons with alcohol use disorders, one group studied 172 individuals with alcohol use disorders of whom 104 had insomnia as determined by the Sleep Disorders Questionnaire [35]. They found that participants with baseline insomnia had longer sleep latency and lower sleep efficiency at an average of approximately 1 month abstinent than those without, suggesting a correspondence between self-report and objective measurement.

#### **Clinical and laboratory correlates of subjective and objective sleep outcomes**

In a small study, increased sleep latency associated with chronic alcohol use was linked with lower overall melatonin levels as well as with a delay in the onset and peak of melatonin [123]. A much larger study found an association between increased sleep latency and decreased sleep efficiency among persons with AUD and sleep disorder breathing [6].

In patients with AUD, insomnia is also correlated with amount of alcohol use [22], severity of alcohol use disorder [35], and self-report of alcohol use as a sleep aid [35]. An association between insomnia and severity of self-reported depression symptoms has also been recognized [35].

#### **Relationship between subjective measurements and clinical outcomes**

Several studies among alcohol AUD subjects have documented the relationship between self-reported insomnia and clinical outcomes. These studies examined the effects of 1 week of abstinence while undergoing inpatient admission (e.g., subjects who self-reported insomnia during this week had higher likelihood of choosing to drink as part of a subsequent inpatient period in which this option was allowed) [182], and showed similar results after following subjects for 3 months post-detoxification (e.g., compared to subjects who did not relapse during this period, subjects who did relapse were more likely to answer “yes” to the statement, “It takes me a long time to fall asleep” from the Nottingham Health Profile [NHP] or, “I sleep badly at night,” as part of their baseline assessments) [76], or after

following subjects for 5 months (e.g., having insomnia based on the Sleep Disorders Questionnaire after 2 weeks of abstinence was a predictor of relapse). Also, subjects who relapsed after 5 months had more baseline complaints of difficulties falling asleep and abnormal sleep than the group who did not relapse [34, 35].

#### **Relationship between objective measurements and clinical outcomes**

Mixed findings implicate objective sleep measurements as predictors of clinical outcomes in AUD. For example, increased sleep latency measured within the first 2 weeks of inpatient admission increased the odds of relapse to alcohol use within the following 5 months [34]. Similarly, increased sleep latency and decreased sleep efficiency after 16 days and 19 weeks of abstinence were associated with lower rates of abstinence at 14 months [69]. However, one study found no difference in sleep latency at 5 days abstinent between persons who subsequently relapsed and those who remained abstinent [82].

Two studies have reported a connection between slow-wave sleep and clinical measures in persons with AUD. Slow-wave sleep time was inversely correlated to the maximum number of withdrawal symptoms reported during subacute withdrawal (8–32 days of abstinence) [83], and lower percent of stage 4 NREM sleep was associated with relapse [34]. However, another study found no difference in slow-wave sleep between relapsers and abstainers [82].

Similar to clinical studies examining sleep latency and SWS, REM sleep measurements appear to be important in clinical outcomes, but with conflicting results. The differences observed here might be consistent with the differences in the measurement of REM sleep in persons with AUD described above. For instance, while one study indicated a positive correlation between low REM% with response rate in a button-press task to obtain an alcoholic drink [8], Gillin et al. showed increased REM% and shorter REM latency upon admission and upon discharge from a four-week admission among relapsers in comparison with abstainers [82]. Another study showed that increased REM latency decreased the odds of relapsing [34], and one study found no connection between REM latency measured at 19 weeks of abstinence and subsequent relapse [69]. The variation in results regarding REM sleep may be due to the different effect that acute and chronic use, have on REM sleep, and be due to changes in REM sleep as the number of days abstinent increases. Another important consideration is that achieving long periods of abstinence (e.g., like 19 weeks) is in general a good predictor of abstinence and does so to a much greater degree than the predictive qualities of other physiological measurements obtained early in abstinence.

#### **Pharmacotherapy options targeting sleep abnormalities**

Because of the profound effects of chronic alcohol use and sleep and the apparent connection between sleep measures and clinical outcome, several studies have examined the role of sleep-promoting medications in treating persons with AUD (for review see [119]). In double-blind, placebo-controlled and other trials, gabapentin has been studied with largely [112, 136, 137] but not entirely [39] positive results. These studies suggest that gabapentin may promote both sleep outcomes and abstinence [137] in persons with alcohol use disorders.

Given the suggestion that melatonin levels are decreased in alcoholics [177, 212], the melatonin receptor agonists ramelteon and agomelatine have been examined in case series. Among patients who had been abstinent for 2–13 weeks, ramelteon was associated with decreased scores on the Insomnia Severity Index (ISI), decreased sleep latency, and increased total sleep time measured by actigraphy [36]. Similarly, agomelatine was associated with improved sleep as measured by the Pittsburgh Sleep Quality Index after 6 weeks [87].

Another potential pharmacotherapeutic agent that has been studied in this population is quetiapine. In a double-blind, placebo-controlled trial, quetiapine was associated with improvements in time awake after sleep onset and subjective insomnia [53]. In addition, a retrospective study showed an improvement on the insomnia subscale of the HAM-D [173] with quetiapine. The effect of quetiapine on alcohol-related clinical outcomes has been mixed, with evidence for improvement in abstinence rates in one study [142], and increased risk of re-hospitalization in another [143].

Trazodone is widely prescribed as a sleep aid in persons with addictions because of its lack of addictive potential. Although studies of trazodone in persons with AUD has shown benefits in sleep measurements [125] in a large, placebo-controlled trial, those benefits on sleep quality did not result in clinical improvement, but rather trazodone was associated with less abstinence during treatment and an increase in drinking after cessation of treatment [79]. Findings like these suggest that the relationship between sleep physiology and alcohol use and relapse is not simple. Rather, treatments directed at sleep that improve qualitative sleep but do not address the underlying physiological changes associated with chronic alcohol use may not be expected to promote abstinence.

Unlike trazodone, the popular benzodiazepine and benzodiazepine-like agents are often avoided in persons with alcohol use disorders because of their addictive potential and the increased risk of toxicity or overdose when these medications are mixed with alcohol [16, 90].

## Cannabis

### Subjective measurements

Like alcohol, cannabis may improve subjective sleep complaints [56], particularly when used over short periods of time. For instance; in studies using self-report questionnaires (e.g., Leeds Sleep Evaluation Questionnaire) participants report greater ease in getting to sleep [50]. However, like alcohol, chronic cannabis use is associated with negative subjective effects on sleep that are manifested most prominently during withdrawal. Notably, these subjective effects are present during discontinuation of cannabis use even among persons who were exposed to low dosages [97], and are common among regular users [61, 188]. Symptoms reported include sleep difficulties [61] such as strange dreams, insomnia, and poor sleep quality. Such symptoms occur in anywhere from 32 % [58] to 76 % [27, 222] of persons experiencing withdrawal. These studies have been conducted in both the inpatient (residential) [61, 97, 98] and outpatient levels of care [42, 44], and in studies with as many as 450 participants [222]. Placebo-controlled studies have examined what happens after discontinuation of oral THC use [97] or after discontinuation of smoked marijuana [98]. Regardless of design, studies of the effects of chronic use have consistently shown reliable and significant changes in subjective reports of sleep during abstinence in comparison to baseline [42].

Among the problems with sleep in chronic cannabis users is the presence of strange dreams [44]. Such dreams typically begin 1–3 days after cannabis discontinuation—when sleep quality is particularly poor [42, 44, 195], peak after 2–6 days, and last 4–14 days [44], coincident with other subjective sleep complaints. However, large studies have found sleep difficulties lasting for longer periods, such 43 days [58], and strange dreams in particular lasting for as long as 45 days [44]. Returning to cannabis use (or using alcohol or other sedatives) to promote sleep is commonly observed [58].

However, the sleep-promoting effect of cannabis is lessened in the chronic user compared to naïve users [50–52, 91], while the negative effects of cannabis on sleep intensify with chronic use as noted above. This scenario leaves the chronic user in a potential catch-22: heavier use of cannabis may be necessary to receive its subjective sleep-promoting effects in the chronic user, but at the same time this increased use contributes to worsening overall sleep and therefore leads to continued and greater use.

### Objective measurements

Studies examining the effect of cannabis on objective sleep measurements obtained either by an experienced observer rating sleep by polysomnography (PSG)

largely confirm the subjective reports. For instance, an observer-rated study showed that administration of 10, 20, or 30 mg of THC decreased total time to fall asleep [60], and a PSG study showed both shorter sleep latency (SL) [150], and decreased time awake after sleep onset (WASO) [160]. However, other studies have not observed a decrease in sleep latency or wake time after sleep onset [75]. One possible explanation for the difference in findings may be related to disparate effects of THC (sleep promoting) and cannabidiol (a non-euphorogenic cannabinoid preferred in some medical preparations), which may increase alertness [150].

Several studies of PSG-measured sleep report increased SWS [25, 75], decreased REM sleep [74, 75, 160], and decreased REM density (e.g., number of eye movements during REM sleep) [74, 75]. However, this pattern is not always replicated [150].

In chronic users of cannabis, the effects of cannabis on objectively measured sleep are notably different. With chronic use, individuals develop tolerance to most of the effects observed in naïve users, including its sleep-inducing effects and slow-wave sleep enhancement [25, 78, 111, 163]. Sleep efficiency is similarly unimproved [163] or worsens [111]. The tolerance to REM sleep changes, however, appears to be relatively muted [75]. However, no consensus exists with respect to REM time and studies have reported decreased, no change [163], or increased [111] REM time.

PSG studies of cannabis withdrawal have demonstrated increases in sleep onset latency and wakefulness after sleep onset [27, 28, 75, 77, 78, 175] (Table 2). Total sleep time, sleep efficiency, and slow-wave sleep time is reduced [1, 27, 28, 75, 78] (Table 1), and REM sleep is increased (REM rebound) [74, 75, 77, 108, 160, 175]. Shorter REM latency has also been reported [27, 77].

Changes in the objective PSG measurements during withdrawal can start as soon as the first night of abstinence (e.g., the decrease in SWS time [74]). Changes during withdrawal are more noticeable among heavy marijuana users (marijuana use  $\geq 5$  times per week over the past 3 months) [27]. With continued abstinence, TST, SE, and amount of REM sleep decline (Table 2), while WASO increases. These disturbances progress over the first 2 weeks of abstinence [28, 44, 120] and persist for more than 45 days into a marijuana abstinence period [44].

There are conflicting reports with regard to REM sleep in sustained abstinence. Initially it appears that REM sleep time increases/rebounds early in abstinence, but decreases as abstinence progresses [28] (Table 2). The reason for this continued worsening of sleep with decreasing REM sleep during abstinence is unclear, but could reflect a pre-existing, underlying sleep problem and/or the long-term effects of chronic use.

### Relationship between subjective and objective outcomes

As noted above, the desirable effects of cannabis on sleep are reported less frequently in chronic cannabis users compared to naïve users [91]. Chronic users also report difficulty sleeping and strange dreams among other symptoms associated with abstinence [11, 28, 43, 58, 175, 194]. These subjective findings have been correlated to longer sleep onset latency, reduced slow-wave sleep, and REM rebound observed in PSG studies [27, 198].

### Clinical and laboratory correlates of subjective and objective sleep outcomes

Sleep difficulties appear to be a predisposing factor for cannabis use, and baseline sleep problems are a significant predictor of later cannabis use, doubling the risk of future use [139, 155, 166, 211, 214]. This latter finding has led some to describe cannabis use as “coping oriented use” [21].

The sleep disturbances encountered in marijuana withdrawal may play a crucial role in treatment outcomes. Higher rates of relapse have been correlated with sleep problems and other withdrawal symptoms [43]. In a study focused on military veterans, Babson et al. showed that poor sleep quality prior to the quit attempt was a predictor of higher rates of later cannabis use [19–21]. Similarly, poor sleep quality during abstinence also contributes to relapse [44, 46, 195]. Evidence from a limited number of studies suggests that objective findings, like increased periodic limb movements during abstinence, are correlated with quantity and duration of cannabis use [28].

### Pharmacotherapy options targeting sleep abnormalities

Sleep disturbances associated with withdrawal improve with oral administration of THC or resumption of cannabis use [42, 44, 45, 95, 97, 108]. THC exerts a dose-dependent effect in reducing withdrawal symptoms [45], but as noted above, the beneficial effects of THC on sleep diminish with chronic use, and chronic use leads to more severe problems with sleep.

Haney et al. found the greatest benefit regarding sleep symptoms and relapse using combination therapy with lofexidine (an alpha-2 agonist) and oral THC. However they did not report any benefit from 10 days of oral THC alone [94]. Nabilone, a FDA-approved synthetic analog of THC, has the potential to reverse withdrawal-related irritability and disruptions in sleep, and promotes abstinence [92]. Nabiximols, a synthetic combination of THC and cannabidiol has a non-significant positive effect on these parameters [10].

The use of valproic acid resulted in no benefit and even some worsening of symptoms in chronic cannabis users

[95, 128]. No definitive benefits have been reported with Lithium [107], nefazodone [96], or bupropion [49, 99].

Subjective and/or objective sleep parameters have been shown to improve with the use of zolpidem [195], mirtazapine [93], gabapentin [135], and quetiapine [57], but none of these agents have conclusively reduced the relapse rate.

## Cocaine

### Subjective measurements

Withdrawal from cocaine is characterized by numerous subjective complaints, including sleep and sleep-related complaints. The first several days to 1 week after cocaine cessation are characterized by sleep disturbances, hypersomnia, bad dreams, depressed mood, psychomotor agitation and retardation, fatigue, and increased appetite [38, 59, 80]. With continued abstinence, however, there is subjective improvement of sleep as well as improvements in other cocaine withdrawal measures [209], with apparent normalization of subjective sleep over the course of several weeks [80].

Numerous studies have indicated an improvement in self-reported sleep quality over the first few weeks of abstinence [13, 55, 81, 138, 147, 148, 153, 172, 209], with improvements in measures such as overall sleep quality, daytime alertness, concentration/confusion, depth of sleep, and energy/fatigue. However, the possibility that such improvements may be related to acclimation to a new environment (e.g., the treatment setting [209]) and not actually reflect good sleep relative to healthy persons [55] has been raised. Possibly providing some answers to these questions, a laboratory study that included self-administration of cocaine either early or late in a 3-week period of abstinence showed that subjective sleep quality was at its worst in the first few days following cocaine use and improved with continued abstinence [148]. In addition, whereas chronic cocaine users show impairment in self-reported but quasi-objective sleep measurement like the Pittsburgh Sleep Quality Index (PSQI), visual analog scale ratings of subjective sleep quality in the third week of abstinence are no different from healthy sleepers [147]. Hence there is evidence that chronic cocaine users have chronically impaired sleep as measured by instruments like the PSQI, that self-reported sleep quality improves with continued abstinence, and that self-reported sleep quality after an extended period of abstinence is similar to that in healthy sleepers. However, this last finding may only show that chronic cocaine users' intrinsic scale for self-report of sleep quality is different from healthy sleepers, with 'good' subjective sleep in chronic cocaine users seemingly good only in comparison with the much worse sleep experience they have at other times.

### Objective measurements

Although self-reported sleep improves following the initial withdrawal from cocaine, polysomnographic findings have consistently shown deterioration in sleep to insomnia-like levels in the same period [13, 81, 104, 121, 138, 145, 148, 152, 192]. The co-occurring deterioration in PSG-measured sleep and improvement in self-reported sleep quality was termed ‘occult insomnia,’ as poor sleep as measured by PSG was associated with poor performance on sleep-dependent learning and other cognitive tasks [148, 149]. These findings suggest that the PSG-measured deterioration in sleep and not the subjective improvement in sleep better reflects what is happening during abstinence from chronic cocaine use, and supports the notion that the intrinsic, subjective scale used by chronic cocaine users to report sleep quality is altered relative to healthy persons.

### Sleep latency

Acute cocaine administration can increase sleep latency [104, 162, 207], but the first few days of abstinence from cocaine in chronic users is associated with short sleep latencies relative to later in abstinence [81, 121, 138, 148, 153, 192], when sleep latency may be as long as 30–60 min or more (Table 2).

### Total sleep time

Total sleep time during abstinence is reduced in chronic cocaine users [147] but appears to be at its greatest sometime in the early abstinence period (first week of abstinence) in laboratory studies including cocaine self-administration [148]. Total sleep time decreases with continued abstinence (Table 2), however [81, 104, 121, 138, 147–149, 153, 162, 192, 207], with total sleep times around the third week of abstinence as low as 300–330 min despite prohibitions against daytime napping and the opportunity to sleep 8 h or more. Sleep efficiency follows a similar pattern, with insomnia-like levels apparent in the third week of abstinence [153]. Limited evidence suggests that chronic cocaine users able to maintain outpatient abstinence for as long as 54 days show some improvement in total sleep time [13].

### Slow-wave sleep

Chronic cocaine users appear to have dramatically diminished slow-wave sleep time relative to age-matched healthy sleepers [13, 147] (Table 2). More limited evidence suggests that slow-wave activity is increased by cocaine self-administration earlier in the day, with a subsequent loss of slow-wave activity in the first several days of abstinence followed by a rebound over the next 2 weeks of abstinence [148]. More substantial evidence indicates that slow-wave sleep time increases modestly

from the first to the third week of abstinence [138], but at 3 weeks of abstinence is still 50 % less than age-matched healthy sleepers [13]. This deficit in slow-wave sleep generation is associated with impaired slow-wave sleep specific, sleep-dependent learning [149], and is consistent with or more profound than similar findings in chronic users of alcohol, cannabis, other stimulants, and heroin [25, 27, 175, 192] suggesting an abnormality in sleep homeostasis [145] that may be common to chronic, regular use of addictive substances.

### Rem

Cocaine administration acutely suppresses REM sleep [104, 162, 207], with a subsequent rebound evident as an increase in REM sleep time and/or percent of total sleep time spent in REM (REM%), and a decrease in REM latency [81, 104, 121, 149, 153, 192, 207]. However, in chronic cocaine users, REM sleep decreases following the rebound, with low REM times observed during the second and third weeks of abstinence [13, 104, 138, 147, 149, 153, 192] (Table 2). This diminished REM sleep time is associated with cognitive consequences like poor procedural learning [149], suggesting an abnormality of REM homeostasis during abstinence from chronic use. Consistent with this idea is the observation that REM latency is higher in the third week of abstinence relative to the first [149] and at 3 weeks abstinence does not differ substantially from healthy sleepers [147] (Table 2), despite low REM sleep time.

### Relationship between subjective and objective outcomes

What is now clearly shown to be a mismatch in subjective and objective experience during acute and subacute abstinence was once perceived as an inconsistency [104, 153]. One possible cause for the mismatch may be dysregulation of the homeostatic sleep drive in chronic cocaine users, wherein the ‘sleepiness’ and other negative effects of increased wakefulness are not experienced subjectively [148]. Additionally, or alternatively, the rebound in delta power after acute withdrawal [148], despite poor sleep and decreased slow-wave sleep time, may improve the subjective experience of sleep quality [122, 148]. The poor subjective experience in acute withdrawal may also be related to the decreased REM latency and increased REM sleep time, leading to increased dreaming [38, 59] and correlated with symptoms of withdrawal [13].

### Clinical and laboratory correlates of subjective and objective sleep outcomes

#### Cognitive correlates of sleep outcomes

Chronic cocaine use is associated with various cognitive performance deficits (e.g., see [152]) that may



predict treatment retention and other outcomes [3–5]. As described briefly above, poor sleep associated with abstinence from chronic use may contribute to poor cognitive performance including decreased attention or vigilance [148, 149, 152]. The most direct associations between poor sleep and cognitive deficits, however, are observed in sleep-dependent procedural learning. In such tasks, overnight learning is strongly correlated with objective sleep measurement, such as slow-wave sleep time [189], REM time [189], and stage 2 (N2) sleep time (M. P. [202]). In chronic cocaine users, similar correlations are present; in nights with relatively normal sleep, normal sleep-dependent learning takes place, but in nights with impaired sleep, such learning is similarly impaired [148, 149]. Hence, sleep abnormalities associated with abstinence from chronic cocaine use may be responsible for significant impairment in normal, sleep-dependent learning, as well as more immediate cognitive function like attention. Intriguingly, cocaine administration is associated with temporary reversal of these deficits [148, 149, 152], further implicating such deficits in risk for relapse.

#### **Relationship between objective measurements and clinical outcomes**

Recent evidence supports the assertion that poor sleep associated with abstinence from cocaine not only impairs cognitive performance, but also contributes to increased cocaine use or relapse [13]. In this study, the homeostatic response to continued abstinence (which was measured as change in slow-wave sleep time from the first week of abstinence to the second or third week) predicted the amount of cocaine self-administered in a laboratory experiment and clinical outcome in a clinical trial. In addition, REM sleep time and total sleep time during the third week of abstinence predicted the amount of cocaine self-administered. In all cases, improvements in sleep were associated with less self-administration or better clinical outcome.

#### **Pharmacotherapy options targeting sleep abnormalities**

Although several medications such as modafinil, topiramate, tiagabine, gaboxadol and vigabatrin [145] have been suggested as potential options for targeting the sleep abnormalities associated with chronic cocaine use, few studies have examined the effects of medications on sleep in chronic cocaine users, and several of the suggested medications have potentially significant safety issues (i.e. tiagabine, gaboxadol, and vigabatrin). Hypothesizing that the REM rebound associated with initial withdrawal from cocaine was caused by dopamine insufficiency [62], Gillin et al. [81, 82] examined the effect of lisuride, a high affinity dopamine D<sub>2,3,4</sub> receptor agonist, on sleep. While lisuride had the desired effect on REM

sleep (decreasing REM% and increasing REM latency), it had no effects on other withdrawal-related phenomenon [81]. In light of the clinical findings in Angarita et al. [13] and the effect of prolonged abstinence on REM sleep, it seems unlikely that reduction in REM sleep time would be beneficial during extended abstinence, but *increasing* REM to normal values could be beneficial.

Another medication that has been tested is tiagabine, a GABA-reuptake inhibitor. Since tiagabine is known to increase slow-wave sleep time, which is implicated in improved cognitive performance in sleep-restricted persons [203], it was hypothesized that tiagabine may improve slow-wave sleep time in chronic cocaine users [146]. While tiagabine had dramatic effects on slow-wave sleep time, sleep architecture appeared unnatural, with slow-wave sleep occurring throughout the sleep period. Additionally, there was no apparent benefit to total sleep time, and no consistent benefit in cognitive performance [146].

Perhaps the most promising, and most studied medication to be tested for correcting sleep abnormalities related to cocaine is modafinil. A stimulant and cognitive enhancer that appears to act at least partially through dopamine transporter blockade, modafinil appears to share some important properties with cocaine while being a relatively safe medication with low abuse potential [140]. In chronic cocaine users, modafinil has been shown to normalize slow-wave sleep time, as well as other sleep parameters [147]. Though effects of modafinil on clinical outcome have been mixed (e.g., [12, 63, 64, 176]), its effects on sleep and its pro-cognitive effects position it as the best candidate at present for a viable pharmacotherapy for cocaine use disorders.

## **Opioids**

### **Subjective measurements**

Short-term opioid use can cause sedation and daytime drowsiness [130, 159, 216, 217]. Dizziness and sleepiness are common side effects of opioid pain medications [41, 109]. With a stable dose, tolerance to the subjective, sedative effects of opioids develops within 2–3 days and some studies find that cognition normalizes after that [103, 129], supporting the notion of tolerance to the sedative effects. However, there is also evidence that unpleasant sedative effects, decreased alertness and increased reaction time in a variety of cognitive tasks continue to be experienced by some patients on a stable dose of narcotic medication [23, 24, 54, 181]. These differences in findings may be related to inconsistencies in how the sedative effects are defined [217].

Xiao et al. [215] studied the quality of sleep in persons with heroin use disorder on early methadone maintenance therapy (MMT) after a median of 5.4 days of

treatment [215]. Patients without pre-existing chronic sleep disturbances demonstrated lower ratings of sleep (Pittsburgh Sleep Quality Index [PSQI]) and daytime sleepiness (Epworth Sleepiness Scale [ESS]) compared to healthy sleepers. Oyefeso et al. [151] reported inadequate sleep quality and quantity as well as difficulty initiating and maintaining sleep in persons with opioid use disorders in early stages of methadone detoxification. Similar studies have shown some increased daytime drowsiness and below normal sleep measures in this patient population [113, 114, 134, 204]. After longer periods of MMT, however, there is some degree of tolerance to these effects [206], and sleep difficulty is shown to be present only in the first 6–12 months of MMT [158, 193].

There is a limited number of reports studying the effects of withdrawal and abstinence from chronic opiate use. Asaad et al. reported insomnia, hypersomnolence, increased sleep latency, and reduced sleep duration in individuals with opioid use disorder after 3 weeks of abstinence [17].

#### **Objective measurements**

Sleep architecture in healthy adults can be significantly altered even after a single dose of oral opioids [67]. Using electroencephalography (EEG) and electromyography (EMG), Kay et al. [117] reported that acute intoxication with heroin, morphine, or methadone resulted in dose-dependent enhancements in arousal during sleep–wake periods. Heroin use demonstrated a stronger effect particularly on reduction of theta waves and REM sleep [117, 204]. Morphine and methadone reduce slow-wave sleep and increase stage 2 sleep [67]. Several studies have shown that acute use of various opioids results in increased REM latency [115, 159], decreased REM sleep time [113–117, 130, 159, 180], increased stage 1 [67, 130, 180] and stage 2 sleep [67], and decreased slow-wave sleep [113–117, 159]. Acute use of opioids also leads to increased sleep latency [116, 130], increased wakefulness after sleep onset (WASO) [113–117, 130, 159, 215], and concomitant decreases in total sleep time (TST) [116, 215] and sleep efficiency (SE) [116, 159, 215].

There is a partial tolerance to the effects of opioids with some evidence for increased REM sleep time in acute use [113, 114, 130], and less pronounced changes in SWS, wakefulness, and arousal observed after chronic use. However, vocalization during REM sleep, delta bursts, and increased daytime sleepiness may be observed in this phase [204]. Tolerance to sleep problems is more prominent in MMT [113, 134, 159, 204], with evidence that persons in treatment for more than 12 months exhibit better recovery sleep following sleep deprivation than persons in shorter-term treatment [193].

Nevertheless, abnormal PSG findings are commonly reported in chronic opioid users despite development of tolerance. These abnormalities include increased sleep latency [100, 185], increased awakening [100, 113, 185, 190], decreased total sleep time [100, 185], and decreased sleep efficiency [100, 190]. Slow-wave sleep time [113, 114, 185, 190] and REM sleep are decreased compared to baseline [113, 185, 190, 205], while duration of stage 2 sleep is increased similar to acute use [190, 205]. Analysis of actigraphy data from patients with prescription opioid use disorders indicated poor sleep in terms of total sleep time, sleep efficiency, sleep latency, total time awake, and time spent moving [100].

Several studies have reported changes in patterns of sleep with progressive abstinence from opiates. At around 5–7 days of acute abstinence from chronic heroin use, Howe et al. reported decreased total sleep time, slow-wave sleep, REM, and stage 2 sleep and increased sleep latency, wake after sleep onset, and REM latency compared to healthy sleepers [101] (Table 2). During the first 3 weeks of abstinence, prolonged sleep latency, decreased sleep efficiency, decreased TST, increased arousal index, increased stage 1 and 2, and decreased slow-wave sleep (SWS) were prominent compared to healthy sleepers [17] (Table 2). After 6 weeks and up to 6 months of abstinence from methadone, there is a rebound increase in SWS and REM time to a higher level than baseline [113, 114, 134].

#### **Relationship between subjective and objective outcomes**

Using PSG data, Xiao et al. showed an inverse relationship between the Epworth Sleepiness Scale (ESS) scores and SWS time in patients with heroin use disorder who were in early methadone treatment [215]. They reported poor initial quality of sleep based on the PSQI scores which were significantly correlated with their methadone dosages [102]. PSQI score were also found to be significantly correlated with average diary-reported sleep time, subjective ratings of feeling rested, and PSG sleep efficiency in MMT patients [179]. Overall the high prevalence of sleep complaints in this population along with documented abnormal objective findings argue that these complaints are more likely to be secondary to pathology rather than sleep misperception.

#### **Clinical and laboratory correlates of subjective and objective sleep outcomes**

##### ***Opioids and sleep disordered breathing***

Acute use of small doses of opioids does not appear to significantly increase the risk for increased sleep-disordered breathing [167, 180]. However, chronic opioid use has been associated with several abnormalities including nocturnal oxygen desaturations, abnormal breathing patterns, and Biot's respiration pattern

which ultimately may lead to hypercapnia and hypoxia [29, 73, 88, 126, 164, 165, 191, 201, 204, 218]. Chronic opioid treatment, particularly with extended release preparations is associated with increased risk of central and obstructive sleep apneas compared to BMI and age-matched controls [73, 88, 141, 190, 200, 201, 204, 205, 208]. Between 30 and 90 % of patients on chronic opioid therapy display signs of central apnea in a dose-dependent fashion [73, 190, 200, 201, 205]. Several studies have indicated that chronic opioid use is an independent risk factor for irregular breathing, central apneas, and hypopneas [88, 154, 200, 201]. Additional abnormalities associated with MMT include sleep-disordered breathing, lower arterial oxygen saturation and higher carbon dioxide concentration [178, 190, 205]. There is a positive correlation between the duration of MMT and plasma methadone levels with frequency of sleep apnea [190, 205].

A multivariate analysis of the relationship between demographic factors, mental health and drug use with sleep disturbances on 225 MMT patients found that depressive and anxious symptoms, greater nicotine use, bodily pain, and unemployment were all significant predictors of poorer global sleep quality [186].

Using PSG, Asaad et al. found that severity of depression in MMT patients was inversely correlated with SWS. They reported that SWS in moderate and severe depression was significantly lower than in milder depressive states. However, duration of opioid abuse or type of opioid did not show a significant correlation with the abnormalities in the sleep profile [17].

#### ***Relationship between subjective measurements and clinical outcomes***

Peles et al. [156] used a logistic regression model and showed that a higher methadone dose (defined as greater than 120 mg/day) was associated with poor sleep quality, higher rate of sleep disturbance, more frequent use of sleeping medications, and higher rate of daytime dysfunction [156]. However in a later study (2009), they found no direct correlation between the methadone dose and worse objective and perceived sleep parameters. Rather they suggested that duration and intensity of opioid abuse before admission to MMT was directly correlated with sleep abnormalities [157].

Quality of sleep in substance users who are trying to quit plays an important role in predicting the treatment outcome and poor sleep quality is associated with higher risk of relapse [40, 204]. Predictive factors for abstinence 1 month after detoxification with naltrexone may include sleeping problems upon discharge and any changes in sleeping problems [66]. In MMT patients, psychiatric disorders, greater nicotine and benzodiazepine use,

bodily pain, and unemployment are associated with poorer global sleep quality [156, 186].

#### ***Relationship between objective measurements and clinical outcomes***

Using PSG, Peles et al. evaluated patients with heroin use disorder who were being treated with high and low dose methadone [157]. Of the objective sleep indices, percentage of non-REM deep sleep (i.e. SWS) inversely correlated with number of years of opioid abuse. They found that a lower percentage of SWS and more years of opioid abuse were observed in the group who received higher methadone dose during MMT.

#### ***Positive effects of opioids on sleep***

Judicious use of opioid medications might improve pain-related sleep disorders [14, 30]. Subjective reports of improved sleep after pain control with extended-release morphine sulfate use to treat patients with chronic hip or knee arthritis are backed by objective evidence obtained from PSG indicating better sleep quality [170]. Opioids have also been used to treat a sleep disorder known as periodic limb movement (PLMS), which is often associated with restless legs syndrome [144].

#### ***Pharmacotherapy options targeting sleep abnormalities***

Modifiable psychological and medical risk factors associated with sleep disturbance should be identified and corrected in order to improve quality of life in drug treatment. Treatment of sleep disorders among MMT patients, particularly in those with psychiatric disorders, benzodiazepine abuse, chronic pain, and patients who are on high methadone dose is of crucial importance.

#### ***Methadone***

Methadone maintenance is widely used and a standard pharmacotherapy for treating patients with opioid use disorders [18, 68, 71, 197, 220]. Chronic methadone use is more commonly associated with tolerance to the sleep problems compared to other opioids [113, 134, 159, 204]. However, more than three-quarters of persons receiving methadone maintenance therapy (MMT) still report sleep complaints [151, 156, 186]. This is complicated by the fact that about 50 % of MMT patients report use of both illicit drugs and legal medications to help with sleep [156, 186]. Methadone and electrostimulation (ES) have been used to treat insomnia in the first 30 days of opioid withdrawal [84]. In the first 2 weeks of withdrawal patients treated with electrostimulation had shorter sleep time and more awakenings than patients receiving methadone. They also found that subjects in the ES group who remained in treatment experienced more sleep disturbance than those who dropped out prematurely. Overall

methadone and ES were not efficient in treating insomnia associated with withdrawal. Stein et al. tested whether trazodone (50 mg/night), one of the most commonly prescribed medications for treatment of insomnia, improved sleep among methadone-maintained persons with PSQI score of six or higher [187]. They found that trazodone did not improve subjective or objective sleep problems in this group of patients.

### **Buprenorphine**

Buprenorphine was FDA approved as a pharmacotherapy for opioid use disorders in 2002. Buprenorphine has the advantage of being available from office-based practices [131]. There are limited numbers of studies looking at the effect of buprenorphine on sleep. One study suggests that buprenorphine is comparable to methadone in improving sleep quality in patients involved in long-term treatment [133]. In another study, forty-two patients with opiate use disorder were treated with either methadone or buprenorphine and gradually tapered down over the course of 2–3 weeks. Buprenorphine-treated patients had 2.5 % lower sleep efficiency and 9 % shorter actual sleep time. These significant group differences were most pronounced with the lowest doses toward the late withdrawal phase [161]. The time course of tapering buprenorphine during detoxification might also play a role in the quantity of sleep. A randomized controlled trial of buprenorphine for detoxification from prescription opioid use evaluated sleep time among patients assigned to receive 1, 2, and 4-week buprenorphine tapers. The 4-week taper group reported significantly less loss of sleep compared to the other groups [70].

In a study of 70 patients with chronic opioid use, the effect of buprenorphine on sleep disordered breathing was measured polysomnographically [72]. Patients in this study tended to be young (mean age of 31.8) and non-obese (mean body mass index  $24.9 \pm 5.9$ ). However, treatment with buprenorphine was associated with mild to severe sleep-disordered breathing in this population, with a substantial rate of associated hypoxemia [72].

Although information on the effect of other medications on sleep in chronic opiate users is limited, Srisurapanont and Jarusuraisin [184] explored the effect of amitriptyline ( $57.7 \pm 12$ /night) versus lorazepam ( $2.1 \pm 0.5$ /night) to treat insomnia in 27 patients with opioid withdrawal in a randomized double-blind study [184]. The Sleep Evaluation Questionnaire and three insomnia items of the Hamilton Depression Rating Scale were used to assess sleep. All aspects of sleep (including ease of getting to sleep, perceived quality of sleep, integrity of early morning behavior following wakefulness and Hamilton Depression Rating Scale insomnia items), except for ease of awakening from sleep, were not significantly different in the two treatment

groups. These findings suggest that apart from the hangover effect, amitriptyline is as effective as lorazepam in the treatment of opioid-withdrawal insomnia.

### **Conclusion**

Overwhelming evidence points to chronic alterations in sleep from chronic use of addictive substances that may be distinct from some or all of the acute effects of those substances. Interestingly, the effects of chronic use on sleep are similar among both CNS stimulants and depressants. Decreased sleep time, increased sleep latency and wake time after sleep onset, and deficiency in slow-wave sleep generation appear to be common to chronic use of alcohol, cocaine, cannabis, and opiates. REM sleep is also affected by acute and chronic use, but may be more sensitive to the pattern or quantity of recent use and time from last use, as results vary more among studies. Also linking these abnormalities are connections with ongoing use and relapse. However, treatment with typical sleep promoting agents that increase sleep time or efficiency by increasing light sleep may be counterproductive. Agents that address deficiency in slow-wave sleep generation and alterations in REM sleep may prove to be more useful in addressing the connection between chronically-altered sleep physiology and ongoing use and relapse, but substantial research still needs to be done to explore this possibility.

### **Authors' contributions**

GA performed the initial literature review and drafted the introduction and alcohol sections and coordinated the work of NE and SH. NE drafted the cannabis and opiate sections. SH drafted the cocaine section. PM oversaw the work of the other authors and re-worked the manuscript into its final form, contributing to each section. All authors read and approved the final manuscript.

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### **Competing interests**

The authors declare that they have no competing interests.

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### **References**

1. Adams PM, Barratt ES. Effect of chronic marijuana administration of stages of primate sleep-wakefulness. *Biol Psychiatry*. 1975;10(3):315–22.
2. Adamson J, Burdick JA. Sleep of dry alcoholics. *Arch Gen Psychiatry*. 1973;28(1):146–9.
3. Aharonovich E, Amrhein PC, Bisaga A, Nunes EV, Hasin DS. Cognition, commitment language, and behavioral change among cocaine-dependent patients. *Psychol Addict Behav*. 2008;22(4):557–62. doi:10.1037/a0012971.

4. Aharonovich E, Hasin DS, Brooks AC, Liu X, Bisaga A, Nunes EV. Cognitive deficits predict low treatment retention in cocaine dependent patients. *Drug Alcohol Depend*. 2006;81(3):313–22. doi:[10.1016/j.drugalcdep.2005.08.003](https://doi.org/10.1016/j.drugalcdep.2005.08.003).
5. Aharonovich E, Nunes E, Hasin D. Cognitive impairment, retention and abstinence among cocaine abusers in cognitive-behavioral treatment. *Drug Alcohol Depend*. 2003;71(2):207–11.
6. Aldrich MS, Shipley JE, Tandon R, Kroll PD, Brower KJ. Sleep-disordered breathing in alcoholics: association with age. *Alcohol Clin Exp Res*. 1993;17(6):1179–83.
7. Allen RP, Faillace LA, Wagman A. Recovery time for alcoholics after prolonged alcohol intoxication. *Johns Hopkins Med J*. 1971;128(3):158–64.
8. Allen RP, Wagman AM. Do sleep patterns relate to the desire for alcohol? *Adv Exp Med Biol*. 1975;59:495–508.
9. Allen RP, Wagman AM, Funderburk FR, Wells DT. Slow wave sleep: a predictor of individual differences in response to drinking? *Biol Psychiatry*. 1980;15(2):345–8.
10. Allsop DJ, Copeland J, Lintzeris N, Dunlop AJ, Montebello M, Sadler C, et al. Nabiximols as an agonist replacement therapy during cannabis withdrawal: a randomized clinical trial. *JAMA Psychiatry*. 2014;71(3):281–91. doi:[10.1001/jamapsychiatry.2013.3947](https://doi.org/10.1001/jamapsychiatry.2013.3947).
11. 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(1–2):123–9. doi:[10.1016/j.drugalcdep.2011.06.003](https://doi.org/10.1016/j.drugalcdep.2011.06.003).
12. Anderson AL, Reid MS, Li SH, Holmes T, Shemanski L, Slee A, et al. Modafinil for the treatment of cocaine dependence. *Drug Alcohol Depend*. 2009;104(1–2):133–9. doi:[10.1016/j.drugalcdep.2009.04.015](https://doi.org/10.1016/j.drugalcdep.2009.04.015).
13. Angarita GA, Canavan SV, Forselius E, Bessette A, Pittman B, Morgan PT. Abstinence-related changes in sleep during treatment for cocaine dependence. *Drug Alcohol Depend*. 2014;134:343–7. doi:[10.1016/j.drugalcdep.2013.11.007](https://doi.org/10.1016/j.drugalcdep.2013.11.007).
14. Argoff CE, Silvershein DI. A comparison of long- and short-acting opioids for the treatment of chronic noncancer pain: tailoring therapy to meet patient needs. *Mayo Clin Proc*. 2009;84(7):602–12. doi:[10.1016/S0025-6196\(11\)60749-0](https://doi.org/10.1016/S0025-6196(11)60749-0).
15. Arnedt JT, Conroy DA, Armitage R, Brower KJ. Cognitive-behavioral therapy for insomnia in alcohol dependent patients: a randomized controlled pilot trial. *Behav Res Ther*. 2011;49(4):227–33. doi:[10.1016/j.brat.2011.02.003](https://doi.org/10.1016/j.brat.2011.02.003).
16. Arnedt JT, Conroy DA, Brower KJ. Treatment options for sleep disturbances during alcohol recovery. *J Addict Dis*. 2007;26(4):41–54. doi:[10.1300/J069v26n04\\_06](https://doi.org/10.1300/J069v26n04_06).
17. Asaad T, Ghanem M, Abdel Samee A, El-Habiby M. Sleep profile in patients with chronic opioid abuse: a polysomnographic evaluation in an Egyptian sample. *Addict Disord Their Treat*. 2011;10(1):21–8.
18. Athanasos P, Smith CS, White JM, Somogyi AA, Bochner F, Ling W. Methadone maintenance patients are cross-tolerant to the antinociceptive effects of very high plasma morphine concentrations. *Pain*. 2006;120(3):267–75. doi:[10.1016/j.pain.2005.11.005](https://doi.org/10.1016/j.pain.2005.11.005).
19. Babson KA, Boden MT, Bonn-Miller MO. The impact of perceived sleep quality and sleep efficiency/duration on cannabis use during a self-guided quit attempt. *Addict Behav*. 2013;38(11):2707–13. doi:[10.1016/j.addbeh.2013.06.012](https://doi.org/10.1016/j.addbeh.2013.06.012).
20. Babson KA, Boden MT, Bonn-Miller MO. Sleep quality moderates the relation between depression symptoms and problematic cannabis use among medical cannabis users. *Am J Drug Alcohol Abuse*. 2013;39(3):211–6. doi:[10.3109/00952990.2013.788183](https://doi.org/10.3109/00952990.2013.788183).
21. Babson KA, Boden MT, Harris AH, Stickle TR, Bonn-Miller MO. Poor sleep quality as a risk factor for lapse following a cannabis quit attempt. *J Subst Abuse Treat*. 2013;44(4):438–43. doi:[10.1016/j.jsat.2012.08.224](https://doi.org/10.1016/j.jsat.2012.08.224).
22. Baekeland F, Lundwall L, Shanahan TJ, Kissin B. Clinical correlates of reported sleep disturbance in alcoholics. *Q J Stud Alcohol*. 1974;35(4):1230–41.
23. Banning A, Sjogren P. Cerebral effects of long-term oral opioids in cancer patients measured by continuous reaction time. *Clin J Pain*. 1990;6(2):91–5.
24. Banning A, Sjogren P, Kaiser F. Reaction time in cancer patients receiving peripherally acting analgesics alone or in combination with opioids. *Acta Anaesthesiol Scand*. 1992;36(5):480–2.
25. Barratt ES, Beaver W, White R. The effects of marijuana on human sleep patterns. *Biol Psychiatry*. 1974;8(1):47–54.
26. Benca RM, Obermeyer WH, Thisted RA, Gillin JC. Sleep and psychiatric disorders. A meta-analysis. *Arch Gen Psychiatry*. 1992;49(8):651–68 (**discussion 669–670**).
27. Bolla KI, Lesage SR, Gamaldo CE, Neubauer DN, Funderburk FR, Cadet JL, et al. Sleep disturbance in heavy marijuana users. *Sleep*. 2008;31(6):901–8.
28. Bolla KI, Lesage SR, Gamaldo CE, Neubauer DN, Wang NY, Funderburk FR, et al. Polysomnogram changes in marijuana users who report sleep disturbances during prior abstinence. *Sleep Med*. 2010;11(9):882–9. doi:[10.1016/j.sleep.2010.02.013](https://doi.org/10.1016/j.sleep.2010.02.013).
29. Bouillon T, Bruhn J, Roepcke H, Hoef A. Opioid-induced respiratory depression is associated with increased tidal volume variability. *Eur J Anaesthesiol*. 2003;20(2):127–33.
30. Brennan MJ, Lieberman JA 3rd. Sleep disturbances in patients with chronic pain: effectively managing opioid analgesia to improve outcomes. *Curr Med Res Opin*. 2009;25(5):1045–55. doi:[10.1185/03007990902797790](https://doi.org/10.1185/03007990902797790).
31. Breslau N, Roth T, Rosenthal L, Andreski P. Sleep disturbance and psychiatric disorders: a longitudinal epidemiological study of young adults. *Biol Psychiatry*. 1996;39(6):411–8.
32. Brower KJ. Alcohol's effects on sleep in alcoholics. *Alcohol Res Health*. 2001;25(2):110–25.
33. Brower KJ. Insomnia, alcoholism and relapse. *Sleep Med Rev*. 2003;7(6):523–39.
34. Brower KJ, Aldrich MS, Hall JM. Polysomnographic and subjective sleep predictors of alcoholic relapse. *Alcohol Clin Exp Res*. 1998;22(8):1864–71.
35. Brower KJ, Aldrich MS, Robinson EA, Zucker RA, Greden JF. Insomnia, self-medication, and relapse to alcoholism. *Am J Psychiatry*. 2001;158(3):399–404.
36. Brower KJ, Conroy DA, Kurth ME, Anderson BJ, Stein MD. Ramelteon and improved insomnia in alcohol-dependent patients: a case series. *J Clin Sleep Med*. 2011;7(3):274–5. doi:[10.5664/JCSM.1070](https://doi.org/10.5664/JCSM.1070).
37. Brower KJ, Krentzman A, Robinson EA. Persistent insomnia, abstinence, and moderate drinking in alcohol-dependent individuals. *Am J Addict*. 2011;20(5):435–40. doi:[10.1111/j.1521-0391.2011.00152.x](https://doi.org/10.1111/j.1521-0391.2011.00152.x).
38. Brower KJ, Maddahian E, Blow FC, Beresford TP. A comparison of self-reported symptoms and DSM-III-R criteria for cocaine withdrawal. *Am J Drug Alcohol Abuse*. 1988;14(3):347–56.
39. Brower KJ, Myra Kim H, Strobbe S, Karam-Hage MA, Consens F, Zucker RA. A randomized double-blind pilot trial of gabapentin versus placebo to treat alcohol dependence and comorbid insomnia. *Alcohol Clin Exp Res*. 2008;32(8):1429–38. doi:[10.1111/j.1530-0277.2008.00706.x](https://doi.org/10.1111/j.1530-0277.2008.00706.x).
40. Brower KJ, Perron BE. Sleep disturbance as a universal risk factor for relapse in addictions to psychoactive substances. *Med Hypotheses*. 2010;74(5):928–33. doi:[10.1016/j.mehy.2009.10.020](https://doi.org/10.1016/j.mehy.2009.10.020).
41. Bruera E, Macmillan K, Hanson J, MacDonald RN. The cognitive effects of the administration of narcotic analgesics in patients with cancer pain. *Pain*. 1989;39(1):13–6.
42. Budney AJ, Hughes JR, Moore BA, Novy PL. Marijuana abstinence effects in marijuana smokers maintained in their home environment. *Arch Gen Psychiatry*. 2001;58(10):917–24.
43. Budney AJ, Hughes JR, Moore BA, Vandrey R. Review of the validity and significance of cannabis withdrawal syndrome. *Am J Psychiatry*. 2004;161(11):1967–77. doi:[10.1176/appi.ajp.161.11.1967](https://doi.org/10.1176/appi.ajp.161.11.1967).
44. Budney AJ, Moore BA, Vandrey RG, Hughes JR. The time course and significance of cannabis withdrawal. *J Abnorm Psychol*. 2003;112(3):393–402.
45. Budney AJ, Vandrey RG, Hughes JR, Moore BA, Bahrenburg B. Oral delta-9-tetrahydrocannabinol suppresses cannabis withdrawal symptoms. *Drug Alcohol Depend*. 2007;86(1):22–9. doi:[10.1016/j.drugalcdep.2006.04.014](https://doi.org/10.1016/j.drugalcdep.2006.04.014).
46. 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(4):362–8. doi:[10.1016/j.jsat.2008.01.002](https://doi.org/10.1016/j.jsat.2008.01.002).
47. Burke CK, Peirce JM, Kidorf MS, Neubauer D, Punjabi NM, Stoller KB, et al. Sleep problems reported by patients entering opioid agonist

- treatment. *J Subst Abuse Treat.* 2008;35(3):328–33. doi:10.1016/j.jsat.2007.10.003.
48. Caetano R, Clark CL, Greenfield TK. Prevalence, trends, and incidence of alcohol withdrawal symptoms: analysis of general population and clinical samples. *Alcohol Health Res World.* 1998;22(1):73–9.
  49. Carpenter KM, McDowell D, Brooks DJ, Cheng WY, Levin FR. A preliminary trial: double-blind comparison of nefazodone, bupropion-SR, and placebo in the treatment of cannabis dependence. *Am J Addict.* 2009;18(1):53–64. doi:10.1080/10550490802408936.
  50. Chait LD. Subjective and behavioral effects of marijuana the morning after smoking. *Psychopharmacology.* 1990;100(3):328–33.
  51. Chait LD, Perry JL. Acute and residual effects of alcohol and marijuana, alone and in combination, on mood and performance. *Psychopharmacology.* 1994;115(3):340–9.
  52. Chait LD, Zacny JP. Reinforcing and subjective effects of oral delta 9-THC and smoked marijuana in humans. *Psychopharmacology.* 1992;107(2–3):255–62.
  53. Chakravorty S, Hanlon AL, Kuna ST, Ross RJ, Kampman KM, Witte LM, et al. The effects of quetiapine on sleep in recovering alcohol-dependent subjects: a pilot study. *J Clin Psychopharmacol.* 2014;34(3):350–4. doi:10.1097/JCP.0000000000000130.
  54. Clemons M, Regnard C, Appleton T. Alertness, cognition and morphine in patients with advanced cancer. *Cancer Treat Rev.* 1996;22(6):451–68.
  55. Coffey SF, Dansky BS, Carrigan MH, Brady KT. Acute and protracted cocaine abstinence in an outpatient population: a prospective study of mood, sleep and withdrawal symptoms. *Drug Alcohol Depend.* 2000;59(3):277–86.
  56. Conroy DA, Arnedt JT. Sleep and substance use disorders: an update. *Curr Psychiatry Rep.* 2014;16(10):487. doi:10.1007/s11920-014-0487-3.
  57. 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(6):993–1002. doi:10.1111/j.1369-1600.2012.00461.x.
  58. Copersino ML, Boyd SJ, Tashkin DP, Huestis MA, Heishman SJ, Dermand JC, et al. Cannabis withdrawal among non-treatment-seeking adult cannabis users. *Am J Addict.* 2006;15(1):8–14. doi:10.1080/10550490500418997.
  59. Cottler LB, Shillington AM, Compton WM 3rd, Mager D, Spitznagel EL. Subjective reports of withdrawal among cocaine users: recommendations for DSM-IV. *Drug Alcohol Depend.* 1993;33(2):97–104.
  60. Cousens K, DiMascio A. (-) Delta 9 THC as an hypnotic. An experimental study of three dose levels. *Psychopharmacologia.* 1973;33(4):355–64.
  61. Crowley TJ, Macdonald MJ, Whitmore EA, Mikulich SK. Cannabis dependence, withdrawal, and reinforcing effects among adolescents with conduct symptoms and substance use disorders. *Drug Alcohol Depend.* 1998;50(1):27–37.
  62. Dackis CA, Gold MS. New concepts in cocaine addiction: the dopamine depletion hypothesis. *Neurosci Biobehav Rev.* 1985;9(3):469–77.
  63. Dackis CA, Kampman KM, Lynch KG, Pettinati HM, O'Brien CP. A double-blind, placebo-controlled trial of modafinil for cocaine dependence. *Neuropsychopharmacology.* 2005;30(1):205–11. doi:10.1038/sj.npp.1300600.
  64. Dackis CA, Kampman KM, Lynch KG, Plebani JG, Pettinati HM, Sparkman T, O'Brien CP. A double-blind, placebo-controlled trial of modafinil for cocaine dependence. *J Subst Abuse Treat.* 2012;43(3):303–12. doi:10.1016/j.jsat.2011.12.014.
  65. Dijk DJ. Slow-wave sleep deficiency and enhancement: implications for insomnia and its management. *World J Biol Psychiatry.* 2010;11(Suppl 1):22–8. doi:10.3109/15622971003637645.
  66. Dijkstra BA, De Jong CA, Krabbe PF, van der Staak CP. Prediction of abstinence in opioid-dependent patients. *J Addict Med.* 2008;2(4):194–201. doi:10.1097/ADM.0b013e31818a6596.
  67. Dimsdale JE, Norman D, DeJardin D, Wallace MS. The effect of opioids on sleep architecture. *J Clin Sleep Med.* 2007;3(1):33–6.
  68. Doversy M, Somogyi AA, White JM, Bochner F, Beare CH, Menelaou A, Ling W. Methadone maintenance patients are cross-tolerant to the antinociceptive effects of morphine. *Pain.* 2001;93(2):155–63.
  69. Drummond SP, Gillin JC, Smith TL, DeModena A. The sleep of abstinent pure primary alcoholic patients: natural course and relationship to relapse. *Alcohol Clin Exp Res.* 1998;22(8):1796–802.
  70. Dunn KE, Saulsgiver KA, Miller ME, Nuzzo PA, Sigmon SC. Characterizing opioid withdrawal during double-blind buprenorphine detoxification. *Drug Alcohol Depend.* 2015;151:47–55. doi:10.1016/j.drugalcdep.2015.02.033.
  71. Eugenio KR. Profound morphine tolerance following high-dose methadone therapy. *J Pain Palliat Care Pharmacother.* 2004;18(4):47–54.
  72. Farney RJ, McDonald AM, Boyle KM, Snow GL, Nuttall RT, Coudreaux MF, et al. Sleep disordered breathing in patients receiving therapy with buprenorphine/naloxone. *Eur Respir J.* 2013;42(2):394–403. doi:10.1183/09031936.00120012.
  73. Farney RJ, Walker JM, Cloward TV, Rhondeau S. Sleep-disordered breathing associated with long-term opioid therapy. *Chest.* 2003;123(2):632–9.
  74. Feinberg I, Jones R, Walker J, Cavness C, Floyd T. Effects of marijuana extract and tetrahydrocannabinol on electroencephalographic sleep patterns. *Clin Pharmacol Ther.* 1976;19(6):782–94.
  75. Feinberg I, Jones R, Walker JM, Cavness C, March J. Effects of high dosage delta-9-tetrahydrocannabinol on sleep patterns in man. *Clin Pharmacol Ther.* 1975;17(4):458–66.
  76. Foster JH, Peters TJ. Impaired sleep in alcohol misusers and dependent alcoholics and the impact upon outcome. *Alcohol Clin Exp Res.* 1999;23(6):1044–51.
  77. Freeman FR. Effects of marijuana on sleeping states. *JAMA.* 1972;220(10):1364–5.
  78. Freeman FR. The effect of chronically administered delta-9-tetrahydrocannabinol upon the polygraphically monitored sleep of normal volunteers. *Drug Alcohol Depend.* 1982;10(4):345–53.
  79. Friedmann PD, Rose JS, Swift R, Stout RL, Millman RP, Stein MD. Trazodone for sleep disturbance after alcohol detoxification: a double-blind, placebo-controlled trial. *Alcohol Clin Exp Res.* 2008;32(9):1652–60. doi:10.1111/j.1530-0277.2008.00742.x.
  80. Gawin FH, Kleber HD. Abstinence symptomatology and psychiatric diagnosis in cocaine abusers. Clinical observations. *Arch Gen Psychiatry.* 1986;43(2):107–13.
  81. Gillin JC, Pulvirenti L, Withers N, Golshan S, Koob G. The effects of lisuride on mood and sleep during acute withdrawal in stimulant abusers: a preliminary report. *Biol Psychiatry.* 1994;35(11):843–9.
  82. Gillin JC, Smith TL, Irwin M, Butters N, Demodena A, Schuckit M. Increased pressure for rapid eye movement sleep at time of hospital admission predicts relapse in nondepressed patients with primary alcoholism at 3-month follow-up. *Arch Gen Psychiatry.* 1994;51(3):189–97.
  83. Gillin JC, Smith TL, Irwin M, Kripke DF, Brown S, Schuckit M. Short REM latency in primary alcoholic patients with secondary depression. *Am J Psychiatry.* 1990;147(1):106–9.
  84. Gossop M, Bradley B. Insomnia among addicts during supervised withdrawal from opiates: a comparison of oral methadone and electrostimulation. *Drug Alcohol Depend.* 1984;13(2):191–8.
  85. Gross MM, Goodenough DR, Hastey J, Lewis E. Experimental study of sleep in chronic alcoholics before, during, and after four days of heavy drinking with a nondrinking comparison. *Ann NY Acad Sci.* 1973;215:254–65.
  86. Gross MM, Hastey JM. The relation between baseline slow wave sleep and the slow wave sleep response to alcohol in alcoholics. *Adv Exp Med Biol.* 1975;59:467–75.
  87. Grosshans M, Mutschler J, Luderer M, Mann K, Kiefer F. Agomelatine is effective in reducing insomnia in abstinent alcohol-dependent patients. *Clin Neuropharmacol.* 2014;37(1):6–8. doi:10.1097/WNF.0000000000000007.
  88. Guilleminault C, Cao M, Yue HJ, Chawla P. Obstructive sleep apnea and chronic opioid use. *Lung.* 2010;188(6):459–68. doi:10.1007/s00408-010-9254-3.
  89. Haario P, Rahkonen O, Laaksonen M, Lahelma E, Lallukka T. Bidirectional associations between insomnia symptoms and unhealthy behaviours. *J Sleep Res.* 2013;22(1):89–95. doi:10.1111/j.1365-2869.2012.01043.x.
  90. Hajak G, Muller WE, Wittchen HU, Pittrow D, Kirch W. Abuse and dependence potential for the non-benzodiazepine hypnotics zolpidem and zopiclone: a review of case reports and epidemiological data. *Addiction.* 2003;98(10):1371–8.
  91. Halikas JA, Weller RA, Morse CL, Hoffmann RG. A longitudinal study of marijuana effects. *Int J Addict.* 1985;20(5):701–11.
  92. 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(8):1557–65. doi:10.1038/npp.2013.54.
93. Haney M, Hart CL, Vosburg SK, Comer SD, Reed SC, Cooper ZD, Foltin RW. Effects of baclofen and mirtazapine on a laboratory model of marijuana withdrawal and relapse. *Psychopharmacology*. 2010;211(2):233–44. doi:10.1007/s00213-010-1888-6.
  94. 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(1):157–68. doi:10.1007/s00213-007-1020-8.
  95. Haney M, Hart CL, Vosburg SK, Nasser J, Bennett A, Zubaran C, Foltin RW. Marijuana withdrawal in humans: effects of oral THC or divalproex. *Neuropsychopharmacology*. 2004;29(1):158–70. doi:10.1038/sj.npp.1300310.
  96. Haney M, Hart CL, Ward AS, Foltin RW. Nefazodone decreases anxiety during marijuana withdrawal in humans. *Psychopharmacology*. 2003;165(2):157–65. doi:10.1007/s00213-002-1210-3.
  97. Haney M, Ward AS, Comer SD, Foltin RW, Fischman MW. Abstinence symptoms following oral THC administration to humans. *Psychopharmacology*. 1999;141(4):385–94.
  98. Haney M, Ward AS, Comer SD, Foltin RW, Fischman MW. Abstinence symptoms following smoked marijuana in humans. *Psychopharmacology*. 1999;141(4):395–404.
  99. Haney M, Ward AS, Comer SD, Hart CL, Foltin RW, Fischman MW. Bupropion SR worsens mood during marijuana withdrawal in humans. *Psychopharmacology*. 2001;155(2):171–9.
  100. Hartwell EE, Pfeifer JG, McCauley JL, Moran-Santa Maria M, Back SE. Sleep disturbances and pain among individuals with prescription opioid dependence. *Addict Behav*. 2014;39(10):1537–42. doi:10.1016/j.addbeh.2014.05.025.
  101. Howe RC, Hegge FW, Phillips JL. Acute heroin abstinence in man: I. Changes in behavior and sleep. *Drug Alcohol Depend*. 1980;5(5):341–56.
  102. Hsu WY, Chiu NY, Liu JT, Wang CH, Chang TG, Liao YC, Kuo PI. Sleep quality in heroin addicts under methadone maintenance treatment. *Acta Neuropsychiatr*. 2012;24(6):356–60. doi:10.1111/j.1601-5215.2011.00628.x.
  103. Jacox A, Carr DB, Payne R. New clinical-practice guidelines for the management of pain in patients with cancer. *N Engl J Med*. 1994;330(9):651–5. doi:10.1056/NEJM199403033300926.
  104. Johanson CE, Roehrs T, Schuh K, Warbasse L. The effects of cocaine on mood and sleep in cocaine-dependent males. *Exp Clin Psychopharmacol*. 1999;7(4):338–46.
  105. Johnson EO, Breslau N. Sleep problems and substance use in adolescence. *Drug Alcohol Depend*. 2001;64(1):1–7.
  106. Johnson LC, Burdick JA, Smith J. Sleep during alcohol intake and withdrawal in the chronic alcoholic. *Arch Gen Psychiatry*. 1970;22(5):406–18.
  107. Johnston J, Lintzeris N, Allsop DJ, Suraev A, Booth J, Carson DS, et al. Lithium carbonate in the management of cannabis withdrawal: a randomized placebo-controlled trial in an inpatient setting. *Psychopharmacology*. 2014. doi:10.1007/s00213-014-3611-5.
  108. Jones RT, Benowitz N, Bachman J. Clinical studies of cannabis tolerance and dependence. *Ann NY Acad Sci*. 1976;282:221–39.
  109. Kantor TG, Hopper M, Laska E. Adverse effects of commonly ordered oral narcotics. *J Clin Pharmacol*. 1981;21(1):1–8.
  110. Kaplan KA, McQuaid J, Batki SL, Rosenlicht N. Behavioral treatment of insomnia in early recovery. *J Addict Med*. 2014;8(6):395–8. doi:10.1097/ADM.000000000000058.
  111. Karacan I, Fernandez-Salas A, Coggins WJ, Carter WE, Williams RL, Thornby JI, et al. Sleep electroencephalographic-electrooculographic characteristics of chronic marijuana users: part I. *Ann NY Acad Sci*. 1976;282:348–74.
  112. Karam-Hage M, Brower KJ. Open pilot study of gabapentin versus trazodone to treat insomnia in alcoholic outpatients. *Psychiatry Clin Neurosci*. 2003;57(5):542–4. doi:10.1046/j.1440-1819.2003.01161.x.
  113. Kay DC. Human sleep and EEG through a cycle of methadone dependence. *Electroencephalogr Clin Neurophysiol*. 1975;38(1):35–43.
  114. Kay DC. Human sleep during chronic morphine intoxication. *Psychopharmacologia*. 1975;44(2):117–24.
  115. Kay DC, Eisenstein RB, Jasinski DR. Morphine effects on human REM state, waking state and NREM sleep. *Psychopharmacologia*. 1969;14(5):404–16.
  116. Kay DC, Pickworth WB, Neider GL. Morphine-like insomnia from heroin in nondependent human addicts. *Br J Clin Pharmacol*. 1981;11(2):159–69.
  117. Kay DC, Pickworth WB, Neider GL, Falcone D, Fishman PM, Othmer E. Opioid effects on computer-derived sleep and EEG parameters in nondependent human addicts. *Sleep*. 1979;2(2):175–91.
  118. Knowles JB, Laverty SG, Kuechler HA. Effects on REM sleep. *Q J Stud Alcohol*. 1968;29(2):342–9.
  119. Kolla BP, Mansukhani MP, Schneekloth T. Pharmacological treatment of insomnia in alcohol recovery: a systematic review. *Alcohol Alcohol*. 2011;46(5):578–85. doi:10.1093/alcalc/agr073.
  120. Kouri EM, Pope HG Jr. Abstinence symptoms during withdrawal from chronic marijuana use. *Exp Clin Psychopharmacol*. 2000;8(4):483–92.
  121. Kowatch RA, Schnoll SS, Knisely JS, Green D, Elswick RK. Electroencephalographic sleep and mood during cocaine withdrawal. *J Addict Dis*. 1992;11(4):21–45. doi:10.1300/J069v11n04\_03.
  122. Krystal AD, Edinger JD, Wohlgenuth WK, Marsh GR. NREM sleep EEG frequency spectral correlates of sleep complaints in primary insomnia subtypes. *Sleep*. 2002;25(6):630–40.
  123. Kuhlwein E, Hauger RL, Irwin MR. Abnormal nocturnal melatonin secretion and disordered sleep in abstinent alcoholics. *Biol Psychiatry*. 2003;54(12):1437–43.
  124. Landolt HP, Gillin JC. Sleep abnormalities during abstinence in alcohol-dependent patients. Aetiology and management. *CNS Drugs*. 2001;15(5):413–25.
  125. Le Bon O, Murphy JR, Staner L, Hoffmann G, Kormoss N, Kentos M, et al. Double-blind, placebo-controlled study of the efficacy of trazodone in alcohol post-withdrawal syndrome: polysomnographic and clinical evaluations. *J Clin Psychopharmacol*. 2003;23(4):377–83. doi:10.1097/01.jcp.0000085411.08426.d3.
  126. Leino K, Mildh L, Lertola K, Seppala T, Kirvela O. Time course of changes in breathing pattern in morphine- and oxycodone-induced respiratory depression. *Anaesthesia*. 1999;54(9):835–40.
  127. Lester BK, Rundell OH, Cowden LC, Williams HL. Chronic alcoholism, alcohol and sleep. In: Gross MM, editor. *Alcohol intoxication and withdrawal I*. New York: Plenum Press; 1973. p. 261–79.
  128. Levin FR, McDowell D, Evans SM, Nunes E, Akerele E, Donovan S, Vosburg SK. Pharmacotherapy for marijuana dependence: a double-blind, placebo-controlled pilot study of divalproex sodium. *Am J Addict*. 2004;13(1):21–32.
  129. Levy MH. Pharmacologic management of cancer pain. *Semin Oncol*. 1994;21(6):718–39.
  130. Lewis SA, Oswald I, Evans JI, Akindele MO, Tompsett SL. Heroin and human sleep. *Electroencephalogr Clin Neurophysiol*. 1970;28(4):374–81.
  131. Li X, Shorter D, Kosten TR. Buprenorphine in the treatment of opioid addiction: opportunities, challenges and strategies. *Expert Opin Pharmacother*. 2014;15(15):2263–75. doi:10.1517/14656566.2014.955469.
  132. Logan RW, Williams WP 3rd, McClung CA. Circadian rhythms and addiction: mechanistic insights and future directions. *Behav Neurosci*. 2014;128(3):387–412. doi:10.1037/a0036268.
  133. Maremmani I, Pani PP, Pacini M, Perugi G. Substance use and quality of life over 12 months among buprenorphine maintenance-treated and methadone maintenance-treated heroin-addicted patients. *J Subst Abuse Treat*. 2007;33(1):91–8. doi:10.1016/j.jsat.2006.11.009.
  134. Martin WR, Jasinski DR, Haertzen CA, Kay DC, Jones BE, Mansky PA, Carpenter RW. Methadone—a reevaluation. *Arch Gen Psychiatry*. 1973;28(2):286–95.
  135. Mason BJ, Crean R, Goodell V, Light JM, Quello S, Shadan F, et al. A proof-of-concept randomized controlled study of gabapentin: effects on cannabis use, withdrawal and executive function deficits in cannabis-dependent adults. *Neuropsychopharmacology*. 2012;37(7):1689–98. doi:10.1038/npp.2012.14.
  136. Mason BJ, Light JM, Williams LD, Drobos DJ. Proof-of-concept human laboratory study for protracted abstinence in alcohol dependence: effects of gabapentin. *Addict Biol*. 2009;14(1):73–83. doi:10.1111/j.1369-1600.2008.00133.x.
  137. Mason BJ, Quello S, Goodell V, Shadan F, Kyle M, Begovic A. Gabapentin treatment for alcohol dependence: a randomized clinical trial. *JAMA Intern Med*. 2014;174(1):70–7. doi:10.1001/jamainternmed.2013.11950.
  138. Matuskey D, Pittman B, Forselius E, Malison RT, Morgan PT. A multistudy analysis of the effects of early cocaine abstinence on

- sleep. *Drug Alcohol Depend.* 2011;115(1–2):62–6. doi:[10.1016/j.drugalcdep.2010.10.015](https://doi.org/10.1016/j.drugalcdep.2010.10.015).
139. Mednick SC, Christakis NA, Fowler JH. The spread of sleep loss influences drug use in adolescent social networks. *PLoS One.* 2010;5(3):e9775. doi:[10.1371/journal.pone.0009775](https://doi.org/10.1371/journal.pone.0009775).
  140. Mereu M, Bonci A, Newman AH, Tanda G. The neurobiology of modafinil as an enhancer of cognitive performance and a potential treatment for substance use disorders. *Psychopharmacology.* 2013;229(3):415–34. doi:[10.1007/s00213-013-3232-4](https://doi.org/10.1007/s00213-013-3232-4).
  141. Mogri M, Desai H, Webster L, Grant BJ, Mador MJ. Hypoxemia in patients on chronic opiate therapy with and without sleep apnea. *Sleep Breath.* 2009;13(1):49–57. doi:[10.1007/s11325-008-0208-4](https://doi.org/10.1007/s11325-008-0208-4).
  142. Monnelly EP, Ciraulo DA, Knapp C, LoCastro J, Sepulveda I. Quetiapine for treatment of alcohol dependence. *J Clin Psychopharmacol.* 2004;24(5):532–5.
  143. Monnelly EP, LoCastro JS, Gagnon D, Young M, Fiore LD. Quetiapine versus trazodone in reducing rehospitalization for alcohol dependence: a large data-base study. *J Addict Med.* 2008;2(3):128–34. doi:[10.1097/ADM.0b013e318165cb56](https://doi.org/10.1097/ADM.0b013e318165cb56).
  144. Montplaisir J, Lapierre O, Warnes H, Pelletier G. The treatment of the restless leg syndrome with or without periodic leg movements in sleep. *Sleep.* 1992;15(5):391–5.
  145. Morgan PT, Malison RT. Cocaine and sleep: early abstinence. *ScientificWorldJournal.* 2007;7:223–30. doi:[10.1100/tsw.2007.209](https://doi.org/10.1100/tsw.2007.209).
  146. Morgan PT, Malison RT. Pilot study of lorazepam and tiagabine effects on sleep, motor learning, and impulsivity in cocaine abstinence. *Am J Drug Alcohol Abuse.* 2008;34(6):692–702. doi:[10.1080/00952990802308221](https://doi.org/10.1080/00952990802308221).
  147. Morgan PT, Pace-Schott E, Pittman B, Stickgold R, Malison RT. Normalizing effects of modafinil on sleep in chronic cocaine users. *Am J Psychiatry.* 2010;167(3):331–40. doi:[10.1176/appi.ajp.2009.09050613](https://doi.org/10.1176/appi.ajp.2009.09050613).
  148. Morgan PT, Pace-Schott EF, Sahul ZH, Coric V, Stickgold R, Malison RT. Sleep, sleep-dependent procedural learning and vigilance in chronic cocaine users: evidence for occult insomnia. *Drug Alcohol Depend.* 2006;82(3):238–49. doi:[10.1016/j.drugalcdep.2005.09.014](https://doi.org/10.1016/j.drugalcdep.2005.09.014).
  149. Morgan PT, Pace-Schott EF, Sahul ZH, Coric V, Stickgold R, Malison RT. Sleep architecture, cocaine and visual learning. *Addiction.* 2008;103(8):1344–52. doi:[10.1111/j.1360-0443.2008.02233.x](https://doi.org/10.1111/j.1360-0443.2008.02233.x).
  150. Nicholson AN, Turner C, Stone BM, Robson PJ. Effect of delta-9-tetrahydrocannabinol and cannabidiol on nocturnal sleep and early-morning behavior in young adults. *J Clin Psychopharmacol.* 2004;24(3):305–13.
  151. Oyefeso A, Sedgwick P, Ghodse H. Subjective sleep-wake parameters in treatment-seeking opiate addicts. *Drug Alcohol Depend.* 1997;48(1):9–16.
  152. Pace-Schott EF, Morgan PT, Malison RT, Hart CL, Edgar C, Walker M, Stickgold R. Cocaine users differ from normals on cognitive tasks which show poorer performance during drug abstinence. *Am J Drug Alcohol Abuse.* 2008;34(1):109–21. doi:[10.1080/00952990701764821](https://doi.org/10.1080/00952990701764821).
  153. Pace-Schott EF, Stickgold R, Muzur A, Wigren PE, Ward AS, Hart CL, et al. Sleep quality deteriorates over a binge-abstinence cycle in chronic smoked cocaine users. *Psychopharmacology.* 2005;179(4):873–83. doi:[10.1007/s00213-004-2088-z](https://doi.org/10.1007/s00213-004-2088-z).
  154. Panagiotou I, Mystakidou K. Non-analgesic effects of opioids: opioids' effects on sleep (including sleep apnea). *Curr Pharm Des.* 2012;18(37):6025–33.
  155. Pasch KE, Latimer LA, Cance JD, Moe SG, Lytle LA. Longitudinal bi-directional relationships between sleep and youth substance use. *J Youth Adolesc.* 2012;41(9):1184–96. doi:[10.1007/s10964-012-9784-5](https://doi.org/10.1007/s10964-012-9784-5).
  156. Peles E, Schreiber S, Adelson M. Variables associated with perceived sleep disorders in methadone maintenance treatment (MMT) patients. *Drug Alcohol Depend.* 2006;82(2):103–10. doi:[10.1016/j.drugalcdep.2005.08.011](https://doi.org/10.1016/j.drugalcdep.2005.08.011).
  157. Peles E, Schreiber S, Adelson M. Documented poor sleep among methadone-maintained patients is associated with chronic pain and benzodiazepine abuse, but not with methadone dose. *Eur Neuropsychopharmacol.* 2009;19(8):581–8. doi:[10.1016/j.euroneuro.2009.04.001](https://doi.org/10.1016/j.euroneuro.2009.04.001).
  158. Peles E, Schreiber S, Hamburger RB, Adelson M. No change of sleep after 6 and 12 months of methadone maintenance treatment. *J Addict Med.* 2011;5(2):141–7. doi:[10.1097/ADM.0b013e3181e8b6c4](https://doi.org/10.1097/ADM.0b013e3181e8b6c4).
  159. Pickworth WB, Neidert GL, Kay DC. Morphinelike arousal by methadone during sleep. *Clin Pharmacol Ther.* 1981;30(6):796–804.
  160. Pivik RT, Zarcone V, Dement WC, Hollister LE. Delta-9-tetrahydrocannabinol and synhexl: effects on human sleep patterns. *Clin Pharmacol Ther.* 1972;13(3):426–35.
  161. Pjrek E, Frey R, Naderi-Heiden A, Strnad A, Kowarik A, Kasper S, Winkler D. Actigraphic measurements in opioid detoxification with methadone or buprenorphine. *J Clin Psychopharmacol.* 2012;32(1):75–82. doi:[10.1097/JCP.0b013e31823f91d1](https://doi.org/10.1097/JCP.0b013e31823f91d1).
  162. Post RM, Gillin JC, Wyatt RJ, Goodwin FK. The effect of orally administered cocaine on sleep of depressed patients. *Psychopharmacologia.* 1974;37(1):59–66.
  163. Prankoff K, Karacan I, Larson EA, Williams RL, Thornby JI, Hirsch CJ. Effects of marijuana smoking on the sleep EEG. Preliminary studies. *JFMA.* 1973;60(3):28–31.
  164. Rawal N, Arner S, Gustafsson LL, Allvin R. Present state of extradural and intrathecal opioid analgesia in Sweden. A nationwide follow-up survey. *Br J Anaesth.* 1987;59(6):791–9.
  165. Ready LB, Loper KA, Nessly M, Wild L. Postoperative epidural morphine is safe on surgical wards. *Anesthesiology.* 1991;75(3):452–6.
  166. Roane BM, Taylor DJ. Adolescent insomnia as a risk factor for early adult depression and substance abuse. *Sleep.* 2008;31(10):1351–6.
  167. Robinson RW, Zwillich CW, Bixler EO, Cadioux RJ, Kales A, White DP. Effects of oral narcotics on sleep-disordered breathing in healthy adults. *Chest.* 1987;91(2):197–203.
  168. Roehrs T, Papineau K, Rosenthal L, Roth T. Ethanol as a hypnotic in insomniacs: self administration and effects on sleep and mood. *Neuropsychopharmacology.* 1999;20(3):279–86. doi:[10.1016/S0893-133X\(98\)00068-2](https://doi.org/10.1016/S0893-133X(98)00068-2).
  169. Roncero C, Grau-Lopez L, Diaz-Moran S, Miquel L, Martinez-Luna N, Casas M. Evaluation of sleep disorders in drug dependent inpatients. *Med Clin (Barc).* 2012;138(8):332–5. doi:[10.1016/j.medcli.2011.07.015](https://doi.org/10.1016/j.medcli.2011.07.015).
  170. Rosenthal M, Moore P, Groves E, Iwan T, Schlosser LG, Dziewanowska Z, Negro-Vilar A. Sleep improves when patients with chronic OA pain are managed with morning dosing of once a day extended-release morphine sulfate (AVINZA): findings from a pilot study. *J Opioid Manag.* 2007;3(3):145–54.
  171. Rundell OH, Williams HL, Lester BK. Sleep in alcoholic patients: longitudinal findings. *Adv Exp Med Biol.* 1977;85B:389–402.
  172. Satel SL, Price LH, Palumbo JM, McDougale CJ, Krystal JH, Gawin F, et al. Clinical phenomenology and neurobiology of cocaine abstinence: a prospective inpatient study. *Am J Psychiatry.* 1991;148(12):1712–6.
  173. Sattar SP, Bhatia SC, Petty F. Potential benefits of quetiapine in the treatment of substance dependence disorders. *J Psychiatry Neurosci.* 2004;29(6):452–7.
  174. Schiavi RC, Stimmel BB, Mandeli J, White D. Chronic alcoholism and male sexual function. *Am J Psychiatry.* 1995;152(7):1045–51.
  175. Schierenbeck T, Riemann D, Berger M, Hornyak M. Effect of illicit recreational drugs upon sleep: cocaine, ecstasy and marijuana. *Sleep Med Rev.* 2008;12(5):381–9. doi:[10.1016/j.smrv.2007.12.004](https://doi.org/10.1016/j.smrv.2007.12.004).
  176. Schmitz JM, Green CE, Stotts AL, Lindsay JA, Rathnayaka NS, Grabowski J, Moeller FG. A two-phased screening paradigm for evaluating candidate medications for cocaine cessation or relapse prevention: modafinil, levodopa-carbidopa, naltrexone. *Drug Alcohol Depend.* 2014;136:100–7. doi:[10.1016/j.drugalcdep.2013.12.015](https://doi.org/10.1016/j.drugalcdep.2013.12.015).
  177. Schmitz MM, Sepandj A, Pichler PM, Rudas S. Disrupted melatonin-secretion during alcohol withdrawal. *Prog Neuropsychopharmacol Biol Psychiatry.* 1996;20(6):983–95.
  178. Sharkey KM, Kurth ME, Anderson BJ, Corso RP, Millman RP, Stein MD. Obstructive sleep apnea is more common than central sleep apnea in methadone maintenance patients with subjective sleep complaints. *Drug Alcohol Depend.* 2010;108(1–2):77–83. doi:[10.1016/j.drugalcdep.2009.11.019](https://doi.org/10.1016/j.drugalcdep.2009.11.019).
  179. Sharkey KM, Kurth ME, Anderson BJ, Corso RP, Millman RP, Stein MD. Assessing sleep in opioid dependence: a comparison of subjective ratings, sleep diaries, and home polysomnography in methadone maintenance patients. *Drug Alcohol Depend.* 2011;113(2–3):245–8. doi:[10.1016/j.drugalcdep.2010.08.007](https://doi.org/10.1016/j.drugalcdep.2010.08.007).
  180. Shaw IR, Lavigne G, Mayer P, Choiniere M. Acute intravenous administration of morphine perturbs sleep architecture in healthy pain-free young adults: a preliminary study. *Sleep.* 2005;28(6):677–82.
  181. Sjogren P, Banning AM, Christensen CB, Pedersen O. Continuous reaction time after single dose, long-term oral and epidural opioid administration. *Eur J Anaesthesiol.* 1994;11(2):95–100.



182. Skoloda TE, Alterman AI, Gottheil E. Sleep quality reported by drinking and non-drinking alcoholics. In: Gottheil EL, editor. *Addiction research and treatment: converging trends*. Elmsford: Pergamon Press; 1979. p. 102–12.
183. Snyder S, Karacan I. Sleep patterns of sober chronic alcoholics. *Neuropsychobiology*. 1985;13(1–2):97–100.
184. Srisurapanont M, Jarusuraisin N. Amitriptyline vs. lorazepam in the treatment of opiate-withdrawal insomnia: a randomized double-blind study. *Acta Psychiatr Scand*. 1998;97(3):233–5.
185. Staedt J, Wassmuth F, Stoppe G, Hajak G, Rodenbeck A, Poser W, Ruther E. Effects of chronic treatment with methadone and naltrexone on sleep in addicts. *Eur Arch Psychiatry Clin Neurosci*. 1996;246(6):305–9.
186. Stein MD, Herman DS, Bishop S, Lessor JA, Weinstock M, Anthony J, Anderson BJ. Sleep disturbances among methadone maintained patients. *J Subst Abuse Treat*. 2004;26(3):175–80. doi:10.1016/S0740-5472(03)00191-0.
187. Stein MD, Kurth ME, Sharkey KM, Anderson BJ, Corso RP, Millman RP. Trazodone for sleep disturbance during methadone maintenance: a double-blind, placebo-controlled trial. *Drug Alcohol Depend*. 2012;120(1–3):65–73. doi:10.1016/j.drugalcdep.2011.06.026.
188. Stephens RS, Babor TF, Kadden R, Miller M, G Marijuana Treatment Project Research. The Marijuana Treatment Project: rationale, design and participant characteristics. *Addiction*. 2002;97(Suppl 1):109–24.
189. Stickgold R, Whidbee D, Schirmer B, Patel V, Hobson JA. Visual discrimination task improvement: a multi-step process occurring during sleep. *J Cogn Neurosci*. 2000;12(2):246–54.
190. Teichtahl H, Prodromidis A, Miller B, Cherry G, Kronborg I. Sleep-disordered breathing in stable methadone programme patients: a pilot study. *Addiction*. 2001;96(3):395–403. doi:10.1080/0965214002005374.
191. Teichtahl H, Wang D. Sleep-disordered breathing with chronic opioid use. *Expert Opin Drug Saf*. 2007;6(6):641–9. doi:10.1517/14740338.6.6.641.
192. Thompson PM, Gillin JC, Golshan S, Irwin M. Polygraphic sleep measures differentiate alcoholics and stimulant abusers during short-term abstinence. *Biol Psychiatry*. 1995;38(12):831–6. doi:10.1016/0006-3223(95)00070-4.
193. Trksak GH, Jensen JE, Plante DT, Penetar DM, Tartarini WL, Maywalt MA, et al. Effects of sleep deprivation on sleep homeostasis and restoration during methadone-maintenance: a [31P] MRS brain imaging study. *Drug Alcohol Depend*. 2010;106(2–3):79–91. doi:10.1016/j.drugalcdep.2009.07.022.
194. Vandrey R, Budney AJ, Kamon JL, Stanger C. Cannabis withdrawal in adolescent treatment seekers. *Drug Alcohol Depend*. 2005;78(2):205–10. doi:10.1016/j.drugalcdep.2004.11.001.
195. Vandrey R, Smith MT, McCann UD, Budney AJ, Curran EM. Sleep disturbance and the effects of extended-release zolpidem during cannabis withdrawal. *Drug Alcohol Depend*. 2011;117(1):38–44. doi:10.1016/j.drugalcdep.2011.01.003.
196. Vitiello M. Sleep, alcohol and alcohol abuse. *Addict Biol*. 1997;2:151–8.
197. Volavka J, Verebey K, Resnick R, Mule S. Methadone dose, plasma level, and cross-tolerance to heroin in man. *J Nerv Ment Dis*. 1978;166(2):104–9.
198. Vorspan F, Guillem E, Bloch V, Bellais L, Sicot R, Noble F, et al. Self-reported sleep disturbances during cannabis withdrawal in cannabis-dependent outpatients with and without opioid dependence. *Sleep Med*. 2010;11(5):499–500. doi:10.1016/j.sleep.2009.12.001.
199. Wagman AM, Allen RP. Effects of alcohol ingestion and abstinence on slow wave sleep of alcoholics. *Adv Exp Med Biol*. 1975;59:453–66.
200. Walker JM, Farney RJ. Are opioids associated with sleep apnea? A review of the evidence. *Curr Pain Headache Rep*. 2009;13(2):120–6.
201. Walker JM, Farney RJ, Rhondeau SM, Boyle KM, Valentine K, Cloward TV, Shilling KC. Chronic opioid use is a risk factor for the development of central sleep apnea and ataxic breathing. *J Clin Sleep Med*. 2007;3(5):455–61.
202. Walker MP, Brakefield T, Morgan A, Hobson JA, Stickgold R. Practice with sleep makes perfect: sleep-dependent motor skill learning. *Neuron*. 2002;35(1):205–11.
203. Walsh JK, Randazzo AC, Stone K, Eisenstein R, Feren SD, Kajy S, et al. Tiagabine is associated with sustained attention during sleep restriction: evidence for the value of slow-wave sleep enhancement? *Sleep*. 2006;29(4):433–43.
204. Wang D, Teichtahl H. Opioids, sleep architecture and sleep-disordered breathing. *Sleep Med Rev*. 2007;11(1):35–46. doi:10.1016/j.smrv.2006.03.006.
205. Wang D, Teichtahl H, Drummer O, Goodman C, Cherry G, Cunningham D, Kronborg I. Central sleep apnea in stable methadone maintenance treatment patients. *Chest*. 2005;128(3):1348–56. doi:10.1378/chest.128.3.1348.
206. Wang D, Teichtahl H, Goodman C, Drummer O, Grunstein RR, Kronborg I. Subjective daytime sleepiness and daytime function in patients on stable methadone maintenance treatment: possible mechanisms. *J Clin Sleep Med*. 2008;4(6):557–62.
207. Watson R, Bakos L, Compton P, Gawin F. Cocaine use and withdrawal: the effect on sleep and mood. *Am J Drug Alcohol Abuse*. 1992;18(1):21–8.
208. Webster LR, Choi Y, Desai H, Webster L, Grant BJ. Sleep-disordered breathing and chronic opioid therapy. *Pain Med*. 2008;9(4):425–32. doi:10.1111/j.1526-4637.2007.00343.x.
209. Weddington WW, Brown BS, Haertzen CA, Cone EJ, Dax EM, Hering RI, Michaelson BS. Changes in mood, craving, and sleep during short-term abstinence reported by male cocaine addicts. A controlled, residential study. *Arch Gen Psychiatry*. 1990;47(9):861–8.
210. Weissman MM, Greenwald S, Nino-Murcia G, Dement WC. The morbidity of insomnia uncomplicated by psychiatric disorders. *Gen Hosp Psychiatry*. 1997;19(4):245–50.
211. Weller RA, Halikas JA. Change in effects from marijuana: a five- to six-year follow-up. *J Clin Psychiatry*. 1982;43(9):362–5.
212. Wetterberg L, Aperia B, Gorelick DA, Gwirtzman HE, McGuire MT, Serafetinides EA, Yuwiler A. Age, alcoholism and depression are associated with low levels of urinary melatonin. *J Psychiatry Neurosci*. 1992;17(5):215–24.
213. Williams HL, Rundell OH Jr. Altered sleep physiology in chronic alcoholics: reversal with abstinence. *Alcohol Clin Exp Res*. 1981;5(2):318–25.
214. Wong MM, Brower KJ, Fitzgerald HE, Zucker RA. Sleep problems in early childhood and early onset of alcohol and other drug use in adolescence. *Alcohol Clin Exp Res*. 2004;28(4):578–87.
215. Xiao L, Tang YL, Smith AK, Xiang YT, Sheng LX, Chi Y, et al. Nocturnal sleep architecture disturbances in early methadone treatment patients. *Psychiatry Res*. 2010;179(1):91–5. doi:10.1016/j.psychres.2009.02.003.
216. Young-McCaughan S, Miaskowski C. Definition of and mechanism for opioid-induced sedation. *Pain Manag Nurs*. 2001;2(3):84–97. doi:10.1053/jpmn.2001.25012.
217. Young-McCaughan S, Miaskowski C. Measurement of opioid-induced sedation. *Pain Manag Nurs*. 2001;2(4):132–49. doi:10.1053/jpmn.2001.25169.
218. Yue HJ, Guilleminault C. Opioid medication and sleep-disordered breathing. *Med Clin North Am*. 2010;94(3):435–46. doi:10.1016/j.mcna.2010.02.007.
219. Yules RB, Lippman ME, Freedman DX. Alcohol administration prior to sleep. The effect on EEG sleep stages. *Arch Gen Psychiatry*. 1967;16(1):94–7.
220. Zaks A, Fink M, Freedman AM. Duration of methadone induced cross-tolerance to heroin. *Br J Addict Alcohol Other Drugs*. 1971;66(3):205–8.
221. Zarcone V. Alcoholism and sleep. *Adv Biosci*. 1978;21:29–38.
222. Zehnder D, Hewison M. The renal function of 25-hydroxyvitamin D3-1 $\alpha$ -hydroxylase. *Mol Cell Endocrinol*. 1999;151(1–2):213–20.