

*Chapter XII*

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## **Substance-Related Sleep Disorders**

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### **Abstract**

The consumption of a wide variety of substances determines, through different mechanisms, the onset of sleep disturbances, which has a considerable impact on the neurobiology of sleep-wake circadian rhythm. Many substances are widely used and easy to find, such as alcohol, nicotine and caffeine and are frequently the cause of degradation in quality and quantity of sleep. Furthermore, substance abuse is often associated with poor sleep hygiene. In this case, the regularity of sleep-wake cycle is affected not only by the direct effect of the substances, but also by the presence of correlated disturbing factors in the sleep environment that do not support the synchronization of circadian cycle [1]. Even illicit substances, both psychostimulants and inhibitors of central nervous system - such as heroin, cocaine and ecstasy - have mechanisms of action that lead to a high potential for dysregulation of sleep. The current literature describes sleep abnormalities related to the use/abuse of many other substances sold on the street market or on the internet: cannabis, hallucinogens, methamphetamine, novel psychoactive drugs, etc. In a considerable number of cases, sleep disturbances are caused by prescribed substances - such as corticosteroids, beta-blockers, benzodiazepines and hypnotics, antidepressants, chemotherapy, etc. - which can adversely affect sleep through several different mechanisms. In particular, a significant impact on the above phenomenon is represented by the long-term use of sedative-hypnotics compounds, mainly benzodiazepines, that may generate a dysregulation of sleep through the onset of dependence patterns [2]. From 3-7% of all sleep disorders are caused by use/abuse of psychotropic substances, and 12-16% do have not an apparent cause. It is possible to hypothesize that a variable percentage of these cases could be drug-related cases, underestimated for various reasons. Furthermore, sleep disturbances and substance use correlate with an increased prevalence of psychiatric disorders. It has been reported that 51% of patients with psychiatric disorders become addicted to at least one substance, and

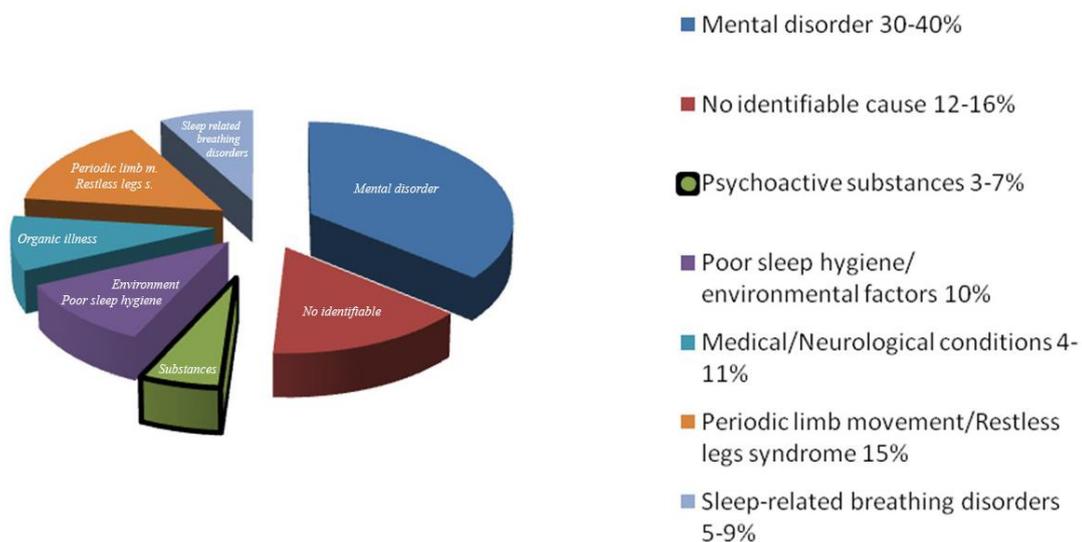
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41-66% of individuals with substance dependence/addiction have a psychiatric disorder. Mental disorders are the main cause of sleep disturbances (e.g. psychiatric illness represents about 30-40% of all cases of insomnia). This fact emphasizes the strong correlation between psychopathology, use/abuse of substances and sleep disorders [3, 4, 5]. The discussion of the molecular and neurobiological mechanisms that bring into connection the use/abuse of substances with qualitative and quantitative alterations of sleep is the central focus of this chapter.

## Introduction

Sleep disorders frequently occur while using psychotropic substances as result of both acute *intoxication* - due to the pharmacodynamic effect - and *withdrawal* syndrome - such a consequence of drug-related neurobiological long-term changes. In fact, the conditions of drug dependence and addiction are a key element in the pathogenesis of substance-related sleep disorders. In particular, drug addiction is a chronically relapsing disorder that is characterized by compulsion to seek and take the drug, loss of control in limiting intake, and emergence of a negative emotional state (e.g. dysphoria, anxiety, irritability that frequently results in insomnia or hypersomnia). This condition reflects a motivational withdrawal syndrome when access to the drug is prevented (defined as Substance Dependence by the DSM-IV-TR) [6]. According to Koob and Volkow, “the occasional but limited use of an abusable drug is clinically distinct from escalated drug use, loss of control over limiting drug intake, and the emergence of chronic critical nature of the distinction between drug use, abuse and dependence has been demonstrated by data showing that approximately 15% of the adult population will engage in non-medical or illicit drug use at some time in their lives, with approximately 3% going on to substance dependence on illicit drugs”. The focus of current studies on drug addiction is shifting to chronic administration and the acute and long-term neuroadaptive changes in the brain that result in relapse and onset of many symptoms (among which insomnia, hypersomnia and parasomnias) [7].



Source: NIH – U.S.A. 2010.

Figure 1. Causes of Sleep Disorders.

Furthermore, sleep disorders can play an important role in the outcome of addiction, sometimes acting as a balance or as a trigger for the relapse. Regarding this, a relevant mechanism is the increase of cortisol and corticosterone resulting in activation of the hypothalamic-pituitary-adrenal axis due to the long-term abuse of substances. These hormones increase brain arousal and frequently cause insomnia [8].

Matching the neurobiological mechanisms of sleep regulation, described in the previous chapters, with the pharmacodynamic knowledge on the effects of drugs and the changes that occur due to the chronic exposure to a substance, we can argue that several neurotransmitter systems are involved in substance-related sleep disorders as a common target. In this context, many studies have reported the role of serotonin in the regulation of sleep (e.g. as a precursor of melatonin - N-acetyl-serotonin - and through the involvement of neurons in the raphe area). As previously shown, even noradrenergic neurons are involved in the regulation of the sleep-wake cycle and N-methyl-D-aspartate (NMDA) transmission. Neurons that release acetylcholine in the pontine reticular formation and in other regions of the basal forebrain (REM-ON neurons), also involved in depression-related insomnia, are involved in substance-related sleep disorders. The GABAergic system, strongly influenced by alcohol and benzodiazepines, is the main inhibitory system of the brain and, therefore, plays a delicate role in regulating the sleep-wake cycle. We must also include the meso-limbic dopamine system, as it is the main target in the onset of addiction, in addition to the meso-cortical and tuber-infundibular dopamine system, which are both involved in the regulation of arousal levels and the circadian cycle. The secretion of melatonin by the pineal gland, usually inhibited by the light of day, would seem to be influenced by the use of several substances. Thus, the suprachiasmatic nucleus of the hypothalamus, usually with circadian pacemaker function for the melatonin secretion and on the entire 24 hour sleep-wake cycle, may be desynchronized by the use of psychotropic substances [2, 8, 9].

On the other hand, from a clinical perspective, when a physician encounters a case of sleep disorder the possibility of use/abuse or the existence of dependence/addiction to psychoactive substances should be investigated. Nonetheless, when there is evidence that the sleep disturbance is directly due to exposure to medications, alcohol or other drugs, it is appropriate to make a diagnosis of substance-induced sleep disorder [6].

In the DSM-IV-TR, this diagnostic category requires fulfillment of the following criteria:

- A. a prominent disturbance in sleep that is sufficiently severe to warrant independent clinical attention.
- B. there is evidence from history, physical examination, or laboratory findings of either 1 or 2:
  1. the symptoms in criterion A developed during, or within a month of, substance intoxication or withdrawal;
  2. medication use is aetiologically related to the sleep disturbance;
- C. the disturbance is not better accounted for by a sleep disorder that is not substance induced. Evidence that the symptoms are better accounted for by a sleep disorder that is not substance induced might include the following: the symptoms precede the onset of the substance use (or medication use); the symptoms persist for a substantial period of time (e.g. about a month) after cessation of acute withdrawal or severe

intoxication, or are substantially in excess of what would be expected given the type or amount of the substance used or the duration of use; or there is other evidence that suggests the existence of an independent non-substance-induced sleep disorder (e.g. a history of recurrent non-substance-related episodes);

- D. the disturbance does not occur exclusively during the course of a delirium;
- E. the sleep disturbance causes clinically significant distress or impairment in social, occupational or other important areas of functioning.

This diagnosis should be made when the sleep symptoms are in excess of those usually associated with the intoxication or withdrawal syndrome and when symptoms are sufficiently severe to warrant independent clinical attention. Sleep disorders can be induced by many substances, including alcohol, amphetamine, caffeine, cocaine, opiates, sedative-hypnotic and/or other substances. It is required to specify the predominant type of sleep disorder, such as *insomnia*, *hypersomnia*, *parasomnia* or mixed type and, as mentioned above, if with onset during intoxication or during withdrawal.

In the following section, we will try to describe the mechanisms that can trigger the sleep alterations for each single substance category.

## Alcohol and Benzodiazepines

Alcohol and benzodiazepines (BDZs) mainly act on  $\gamma$ -aminobutyric acid receptor type A (GABA-A-R). Alcohol also activates nicotinic receptors for acetylcholine, serotonin type 3 receptors (5-HT-3-R) and inhibits glutamate and calcium channel voltage-dependent receptors. Therefore, both alcohol and BDZs produce similar sedative-hypnotic effects and can influence the sleep cycle in terms of hypersomnia or parasomnia - during acute administration - and insomnia or parasomnia after discontinuation of intake or as a consequence of habituation [10]. Alcohol is one of the cultural habits of our society and, unfortunately, is widely used from a young age. BDZs are the most widely prescribed class of psychoactive drugs worldwide. Both can produce addiction. Therefore, screening for current or previous alcohol use/abuse or BZD use is essential in evaluating sleep disorder.

The acute effect of alcohol intake is dose-related and frequently causes drowsiness. As for all the substances described below, the effect varies from individual to individual, and in cases of strong intoxication can lead to coma and death. Therefore, when an individual starts drinking alcohol, and after a long time as well, he/she can develop alcohol-induced hypersomnia.

Even if alcohol intake in the evening is generally associated with an increased ease of falling asleep (i.e. a decreased latency to induction of sleep), alcohol has negative effects on the architecture of sleep. In particular, the use of alcohol is associated with the decrease in the duration of the cycles of REM sleep and deep sleep (stage 4) and therefore is related to increased fragmentation of sleep, as well as longer and more numerous awakening episodes. Considering this, it can be argued that alcohol consumption causes insomnia in the central and late phases of sleep [2]. According to the literature, chronic alcohol assumption (with subsequent habituation and withdrawal when access is prevented) can produce long-lasting changes in neurotransmission, and particularly upon the inhibitory function - involving the  $\gamma$ -

aminobutyric acid type A receptors (GABA-A-R) – that are directly related to the onset of sleep disturbances.

The propensity for dependence on alcohol involves both brain reward mechanisms and withdrawal syndrome, leading to increased consumption. Clinical studies have shown that poor objective sleep during the first two weeks of abstinence predicts relapse to alcohol five months after treatment.

Moreover, withdrawal syndrome frequently includes sleep disorders and tolerance to the sedative actions of alcohol and sleep aids. In a rat model of alcohol dependence, involving chronic intermittent ethanol administration, with multiple episodes of intoxication and withdrawal, it is been possible to deduce that multiple withdrawals produce a kindling-like phenomenon. It is also been demonstrated that behavioral changes are induced by a single dose of alcohol and result from changes in subunit composition, subcellular location, pharmacology and function of GABA receptors. In fact, ethanol-sensitive extrasynaptic  $\alpha 4/\delta$ -containing GABA-R-mediated tonic inhibitory currents are rapidly down-regulated, followed by a slower down-regulation of benzodiazepine-sensitive  $\alpha 1/\gamma 2$ -mediated inhibitory synaptic currents and increased compensatory  $\alpha 4/\gamma 2$  synaptic GABA-R currents in parallel with increased sensitivity to low mM concentrations of ethanol. While these changes are transient and normalize in a few days, chronic intermittent ethanol exposure (>30 doses) makes remodeling of GABA receptors persistent. In consequence of that, it is possible to affirm that GABA receptor plasticity is essential to the development of alcohol dependence, and at the same time provide a model for sleep disorders in chronic ethanol consumers or ex-consumers [11]. From a clinical point of view, the above fact leads to the appearance of strong/progressive chronic insomnia in long-time alcohol consumers.

Many studies have described secondary forms of REM sleep behavior disorder (a sleep parasomnia characterized by enactment of dream content during REM-sleep associated with loss of muscle atonia) or with narcolepsy, which are associated with neurodegenerative diseases belonging to the model of glutamate-related neurotoxicity or to  $\alpha$ -synucleinopathies. However, RBD (REM behavior disorders) may occur in subjects with a history of alcohol abuse or withdrawal [12]. Furthermore, alcohol use is also related to the onset of sleep-disordered breathing, as consequence of obstructive sleep apnea syndrome or internal disorders such as gastro-esophageal reflux [13].

A similar pharmacodynamic and clinical profile may be observed with the acute or chronic use of BDZs. In fact, this category of drugs and alcohol often results in cross-tolerance and cross-dependence. BZDs early users often show sleepiness or hypersomnia and then progress over time toward a state of altered mixed sleep patterns (insomnia alternating with hypersomnia).

The chronic use of BDZs is strictly related to the high prevalence of sleep disorders. BDZs initially result in a reduction of nocturnal awakenings and a prolongation of the total hours of sleep by changing the architecture of sleep, with a strengthening of high frequency electroencephalogram waves and a reduction of slow wave sleep. This is the main reason why these molecules are commonly used in the treatment of insomnia.

However, the subsequent occurrence of tolerance – mainly due to changes in GABA inhibitory neurotransmission - and/or the discontinuation of BDZs intake, with the consequence of rebound phenomenon, may be the cause of sleep disorders, particularly the insomnia type [14].

## Nicotine and Caffeine

Nicotine and caffeine are the most consumed psychostimulant drugs worldwide, and at the same time are easy to find in Western countries. The World Health Organization estimated that the prevalence of smoking in Europe is 28.6% (with a large gender difference: 40% among men and 18.2% among women), and that the prevalence of caffeine users is higher than nicotine [15]. According to their wide diffusion, both substances have a high potential for inducing addiction and sleep disorders. At high doses, they are highly toxic and frequently induce insomnia.

Usually, nicotine is taken through cigarette smoke, but is also present in a wide variety of products used for smoking cessation (trans-dermal patches, chewing gum, inhaler and others) and insecticides. The average content of nicotine in a cigarette is 10-20 mg/g of tobacco and by smoking one cigarette the user absorbs about 1-3 mg of nicotine, depending on the mode of "suction" of the smoke and the absorption capacity. For each "shot" in a matter of seconds (about 7 seconds), the substance is absorbed through the lungs and to a lesser extent by the pharyngeal and gastrointestinal mucosa. Its half-life in plasma is approximately 1.5-3 hours, while the half-life of its principal metabolite, cotinine, is around 12-20 hours [16]. Plasma cotinine levels correlate negatively with slow wave sleep in smokers, and subjective quality of sleep is impaired in smokers compared with non-smokers [17]. Nicotine and cotinine work in the CNS by binding to nicotinic acetylcholine receptor (nAChR) expressed in the meso- limbic system and determine a dopamine spike in the nucleus accumbens shell.

High doses of nicotine can produce different symptoms, including agitation and insomnia. The current literature describes the occurrence of some cases of nicotine poisoning [16]. Nicotine activates, on a massive scale, the mesolimbic reward pathway, resulting in an increase of dopaminergic transmission in these areas - through activation of cholinergic receptors (pre-synaptic nicotinic receptors) on dopaminergic neurons, projecting to the nucleus accumbens - producing a sense of gratification and temporary alleviation of negative moods.

We premised that the nicotine reaches the central nervous system in few seconds, determining its pharmacological effect. Thus, each single aspiration constitutes a positive reinforcement. With 10 aspirations per cigarette, a smoker of a pack/day reinforces the habit of smoking 200 times a day. Nicotine quickly generates tolerance and withdrawal [10]. This is the main reason for the onset of sleep disorders in nicotine addicted individuals, and sleep disturbances are also a known risk factor for early relapse after initial tobacco abstinence.

Heavy smokers (>20 cigarettes/day), in order to fight withdrawal because of the short half-life of nicotine, wake up during the night to smoke and restore normal levels of nicotine in the blood, giving rise to a form of secondary insomnia based on withdrawal syndrome. Furthermore, nicotine induces potent inhibition of monoamine oxidase B (MAO-B) and therefore, insomnia in heavy smokers is also supported by a reduced degradation of catecholamines in the brain.

In a polysomnography (PSG) sleep characteristics study, smokers showed a shorter sleep period time, longer sleep latency, higher rapid eye movement sleep density, more sleep apneas and leg movements in sleep than non-smokers (insomnia-like sleep impairments) [17].

Another relevant factor to consider when evaluating sleep problems is the occurrence of mental disorders. As previously mentioned, this factor correlates with both the trend to

use/abuse cigarettes and insomnia, making it difficult to distinguish between primary and secondary forms of sleep disorders in this population.

Another link between use of cigarettes and sleep disorders (both parasomnia and insomnia type associated with daytime sleepiness) is the occurrence of chronic obstructive pulmonary disease, frequently present in heavy smokers. Airway obstruction generates the phenomena of obstructive apnea during sleep, often associated with the occurrence of both dyssomnias and parasomnias [18].

All these findings suggest that it is important for sleep researchers to always control smoking status in their analyses.

Caffeine (1,3,7-trimethylxanthine) is a mild psychostimulant contained in plants of coffee, cocoa, tea, cola, guarana, mate, etc., and inside beverages made from them, as well as in many analgesic compounds. This natural alkaloid, due the widespread use of beverages in which it is contained, is largely the most used psychoactive substance. Caffeine blocks, through competitive antagonism, adenosine receptors on membranes thereby increasing the secretion of norepinephrine in several brain areas. The dose of caffeine contained in consumer beverages depends on the concentration of the infusion and quality of the product. On average, a cup of coffee contains 90-100 mg of caffeine, a cup of tea about 50 mg, a can of cola 35 mg; some energy drinks contain 80 mg of caffeine per can. The pharmacological effects of caffeine include the appearance of anxiety, tachycardia, tremor, agitation, and insomnia. There are death reports regarding caffeine in subjects taking about 10 grams (the equivalent of 100 cups of coffee or 50 tablets of 200 mg). Regular consumers of caffeine develop tolerance that results in weakening of the stimulating effect, and simultaneously in a heightened sensitivity to adenosine. Subsequent symptoms include anxiety, irritability, and insomnia. However, the most frequent means through which caffeine generates insomnia is the appearance of its acute effects after consumption. Caffeine has a slow absorption in the digestive tract and a half-life of 5 hours. Therefore, the ingestion of coffee, energy drinks (such as Red Bull, Planet Energy, Coca-Cola) or other beverages containing caffeine later than the early afternoon can cause, because of its stimulating effect, marked insomnia and other sleep disorders. In rare cases, abuse of caffeine meets criteria for addiction, including the unsuccessful attempt to reduce the dose, loss of control in use or prolonged use despite the presence of harmful effects on the user [10, 19]. Furthermore, sleepiness associated with the discontinuation of caffeine assumption is a very frequent occurrence in users of this substance.

## **Cocaine and Other Psychostimulants (MDMA, Methamphetamine)**

Considering that the use of psychostimulants causes sleep disturbance primarily through the acute effect, during the intoxication, we will try to review all the neurobiological mechanisms that can affect sleep in stimulant abusers. In fact, stimulant-related sleep disturbances are very common in clinical practice. The most frequent cases of this condition are linked to the abuse of crack and hydrochloride cocaine, MDMA (ecstasy), other ecstasy-like compounds, methamphetamine (crystal ice or shaboo) and katinons. Due to their considerable acute stimulating effect on dopaminergic and noradrenergic neurotransmission,

these substances generate, among other symptoms, increase of arousal, euphoria and a decreased need for sleep.

Chronic cocaine abusers may feel they are sleeping better during early abstinence, but objective measures show that the opposite happens. A team of NIDA-funded addiction and sleep researchers at the Yale and Harvard Schools of Medicine found evidence of insomnia on days of taking the drug and after 2-3 weeks of abstinence. The researchers believe that cocaine may impair the brain's ability to gauge its own need for sleep, and patients' ability to benefit from early treatment may suffer as a result. After 14 to 17 days of abstinence, the study group exhibited sleep deficits on several measures, relative to healthy, age-matched peers who participated in prior studies. For example, they had less total sleep time (336 versus 421-464 minutes) and took longer to fall asleep (19 versus 6-16 minutes). The time participants took to fall asleep and their total time asleep transiently improved during the first week of abstinence, but then reverted to the patterns recorded on days of cocaine taking. On abstinence days 14-17, participants took an average of 20 minutes to fall asleep (from a low of 11) and slept 40 minutes less than their minimum. Slow-wave sleep rose during a binge and on abstinence days 10-17. Unlike most people with chronic insomnia, cocaine abusers do not perceive sleep problems and may not ask clinicians for treatment to improve sleep. Furthermore, the insidious nature of cocaine-related insomnia may directly trigger relapse in addicted individuals, who may take cocaine to improve sleep-related cognitive functioning deficits. Some medications – such as tiagabine and modafinil - can improve cognitive performance and restore sleep in cocaine abusers. In fact, sleep deprivation constitutes an unmet public health problem in the general population. These findings highlight this important problem in cocaine abusers [20, 21].

MDMA-ecstasy works by binding to the type 2 serotonin receptor (5-HT-2). Ecstasy users report a variety of disorders after taking the drug, including sleep disorders. However, mechanisms that link ecstasy use to sleep disorders - such as sleep domains involved or factors that might predict that ecstasy users may have poor sleep quality and / or excessive daytime sleepiness – are not entirely known [22]. In a study on 395 recreational ecstasy users, about 70% reported sleep disturbance.

Although the frequency of ecstasy use did not affect the degree of reported sleep disturbance, participants who used larger amounts of ecstasy had poorer sleep. In addition, participants who perceived harmful consequences arising from their ecstasy use or had experienced remorse following ecstasy use had poorer sleep. Clinically relevant levels of sleep disturbance were still evident after controlling for polydrug use. Risk factors for poor sleep quality were younger age, injury following ecstasy use and having been told to cut down on ecstasy use.

According to a recent study by Di Iorio et al. [23], sleep disturbance are related to the status of serotonin receptors in the cerebral cortex of a group of MDMA young women consumers. The use of this substance causes a chronic reduction of serotonergic transmission by increasing the number of 5-HT-2A receptors in the occipito-temporo-parietal, frontal, fronto-parietal and fronto-limbic areas even in cases of occasional or recreational ecstasy intake. The degree of functional impairment correlated proportionally with both the increase in number of 5-HT-2A receptors and early age of intake of the substance. In addition, the phenomenon does not seem to decrease with abstinence. This is considered an important neurobiological base for sleep disorders in MDMA consumers.

There is evidence of methamphetamine-induced sleep disturbances in both adolescents and adults. Cloak and co-workers have shown, in a magnetic resonance spectroscopy study, that teenage users of methamphetamine have reduced levels of choline compounds at the level of the anterior cingulate cortex. This finding would seem to interfere with the inhibitory functions of the Stroop Test and with a regular alternation in the sleep-wake cycle, as well as a disturbance in the normal brain maturation [24]. At any rate, various methamphetamine and derivatives induced brain damage have been extensively described and, from a clinical point of view, were all related to the presence of sleep disorders. Using both structural and functional neuroimaging, it has been amply demonstrated that the strong use of methamphetamine is related to long-term alterations of the serotonergic and dopaminergic systems [25, 26].

The main areas affected are those involved in selective attention (striatum, prefrontal cortex and amygdala) and memory processes (hippocampus). A picture of general hypertrophy of the white matter with decreased gray matter related to sleep disturbance has also been clearly shown.

## Cannabis

Cannabis use is widespread in Europe and the rest of the world. The rate of lifetime prevalence in individuals between 15 and 64 years is more than 30% in countries such as Italy and the United Kingdom [27]. A proportion of cannabis users start smoking as an attempt to self-medicate states of hyper-arousal or insomnia in individuals with hyperthymic, cyclothimic or irritable type temperament [28]. Other individuals start smoking for reasons that relate to social interaction with a peer group. However, subsequent cases of sleep disturbance arising from use of cannabis have been described, and the above premise should not be viewed as a master key for the use of this substance treating sleep disorders. Cannabis acts by binding to specific receptors for endogenous cannabinoids (anandamide, 2-arachidonoylglycerol and subsequently 2-arachidonyl glyceryl ether, virodamine, N-arachidonyldopamine, palmitoilethanolamine) located in several regions around the brain. Many studies have shown metabolic changes of CNS resulting from the use of cannabis. In a study by 4 Tesla proton magnetic resonance spectroscopy (H1-MRS) in two-dimensional sequences (2D) it was possible to quantify cannabis metabolites at the level of the basal ganglia, thalamus, cortex and white matter in individuals with cannabis addiction. It was possible to highlight an imbalance in the relationship between inositol and creatine compared to the control group of cannabis non-smokers. Furthermore, this imbalance would have been associated with the onset of behavioral and affective disorders (including sleep disorders), often referred by cannabis users, especially if young males [29]. In another study by Vaidya et al., the difficulty in falling asleep (initial insomnia) of young people cannabis addicts abstained from the assumption of cannabis for at least 24 hours is highlighted. In this study, the great difficulties of these individuals to make decisions are also described, due to an alteration in the ventral medial prefrontal cortex (vmPFC). From the results of positron emission tomography (PET) it can be noticed that these individuals likely use larger areas of the brain, with greater cognitive effort, to make decisions and choices [30]. Therefore, the

onset of insomnia during periods of abstinence constitutes a reinforcement to the onset of cannabis addiction.

## Opiates

As described for other substances with a sedative effect, heroin and other opiates (such as codeine, methadone/buprenorphine) may induce hypersomnia - as a result of acute intoxication - and insomnia when access to the substance is prevented - during withdrawal - or as a consequence of habituation. Cases of parasomnias associated with the use of opiates have also been described. Opiates dependency is the strongest and most relevant withdrawal syndrome in clinical practice and frequently causes sleep disorders. Heroin and other opiates act by binding different types of opioid receptors ( $\mu$ -type,  $k$ -type and  $\delta$ -type) in the CNS. The onset of insomnia and parasomnias in chronic opiates users is due to the emergence of alterations that go beyond the up / down regulation of opioid, dopaminergic and GABAergic receptors. According to Nestler et al., it would seem that there are modifications in gene expression that cause qualitative and quantitative changes in addicted neurons. The cascade of signal transduction via cAMP appears compromised, as well as that of phospholipase A2. A regulatory protein of gene transcription at the neuronal level, CREB (cAMP-related element binding), is the main marker of biological processes induced neuronal adaptation after taking long-time heroin. CREB determines an imbalance by activating a massive transcription of genes that encode for dynorphin (endogenous ligand of the  $k$  opioid receptors). This imbalance induces, becoming stable over time, insomnia and dysphoria in individuals with heroin addiction [31]. Based on the above information, also considering the addiction as a chronic relapsing disorder, it can be assumed that sleep disorders (particularly insomnia and parasomnia) are to be expected in individuals with past or current use of opiates, whenever they do not receive adequate treatment with substitution compounds (methadone, buprenorphine). This clinical element affects the rate of relapse and often leads to a switch to other drugs, such as alcohol, cocaine, cannabis, etc. Because of the frequent comorbidity with sleep disorders, it is necessary to prescribe pharmacotherapy for opiate dependence. It is worth remembering that it is necessary to set up a program for long-term treatment (called maintenance) with opioid receptor agonists. The gold standard drugs are methadone and buprenorphine, the latter in single formulation or in combination with naloxone in a proportion of 4:1. The following four therapeutic phases are indicated: induction, stabilization, maintenance, and interruption (optional) under medical monitoring.

## Other Prescribed Compounds

Many studies have reported on sleep disturbances caused by prescribed substances other than benzodiazepines. The most frequent cases in clinical practice involve *corticosteroids*, *beta-blockers*, *antidepressants* and *chemotherapy*, which can adversely affect sleep through several different mechanisms. Therefore, in the anamnesis regarding individuals with insomnia, hypersomnia and parasomnias it is necessary to screen for these compounds and, when present, to determine any correlation with the sleep disorder [1, 10, 32, 33]. To avoid a

discussion beyond the scope of this chapter, we have only listed these categories of prescription medications, referring to specific publications that can clarify the mechanisms through which they induce sleep disorders.

## **Novel Psychoactive Drugs**

A new trend has to be considered in the evaluation of sleep disorders that affects mostly teenagers and young adults. According to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), the widespread use of new psychoactive substances is today a phenomenon of considerable epidemiological importance [34]. Approximately 600 new compounds - new molecules or new psychoactive compositions – are circulating on the web and street market [35]. For many of these compounds, still poorly studied, an association with sleep disorders is been highlighted. A good example of a novel psychoactive drug, which can be used as a paradigm, is mephedrone. This is a synthetic form of the active substance present in the plant Khat (*Catha Edulis* Forsk). The plant, of varying sizes (which vaguely resembles an asparagus that can grow up to several meters), is widely chewed in East Africa and Yemen for its stimulant effects. These effects are due to the presence of an alkaloid that is pharmacologically similar to amphetamine, called cathinone. In addition to its stimulating properties, cathinone is strongly anorectic and induces insomnia. Khat is widely distributed within communities from these countries, after having been introduced to different parts of Europe. Mephedrone (4-methyl-meth-cathinone or 4-MMC, street/internet name “meow meow”) appeared around 2007 and its effects have been largely associated with those of cocaine, amphetamines and ecstasy. The molecule is sold at a low price on the web in the form of crystalline powder or capsules (5 euro for a 250 mg capsule) formally used as fertilizer or as bath salts, always with the words "not for human consumption" (forbidden consumption). The request for mephedrone on the web has increased exponentially over the past years, making it necessary in some countries to ban sales as a plant fertilizer or a salt bath (in the UK it has been illegal since April 2010). On the web, however, there are also instructions for use as a recreational drug. Several deaths related to the misuse of mephedrone in Europe have been reported. It is usually taken on an empty stomach if swallowed or inhaled, but there have been reports in which it was smoked or taken intravenously. The mean dose indicated by consumers is between 100 and 500 mg, but assumptions with doses greater than 4 grams have been recorded. The desired effect, which occurs within 10-20 minutes and reaches a peak after about an hour, and then ceases after a further two hours, consists of an elevation of mood, with euphoria, increased empathy and self-esteem, fatigue reduction and enhancement of sensory experience, up to illusions or hallucinations. Adverse symptoms are frequent after taking mephedrone, and include strong insomnia and other sleep disturbances.

Another example of novel psychoactive drugs related to the onset of sleep disorders are the “spice drugs”. These are composed of a similar texture to dried plants, formally sold on the web as air fresheners, inside envelopes of varying colors. These compounds contain doses of synthetic cannabinoids and produce a boosted cannabis-like effect.

GBL-GHB (liquid ecstasy) is to be counted, along with flunitrazepam and ketamine, among the “date-rape drugs”. GHB abuse can lead to hypersomnia, during acute intoxication, and insomnia in consequence of abstinence.

**Table 1. Synopsis of the effect of substances on sleep**

	INSOMNIA	HYPERMOMNIA	PARASOMNIA
Alcohol and Benzodiazepines	<i>Chronic Use Withdrawal</i>	<i>Intoxication Chronic Use</i>	<i>Intoxication Chronic Use Withdrawal</i>
Nicotine	<i>Withdrawal</i>	-	<i>Intoxication Withdrawal</i>
Caffeine	<i>Intoxication</i>	<i>Withdrawal</i>	<i>Intoxication Withdrawal</i>
Cocaine	<i>Intoxication Chronic Use Withdrawal</i>	<i>Withdrawal</i>	<i>Intoxication Chronic Use Withdrawal</i>
MDMA and Amphetamines	<i>Intoxication Chronic Use Withdrawal</i>	<i>Withdrawal</i>	<i>Intoxication Chronic Use Withdrawal</i>
Cannabis	<i>Withdrawal</i>	<i>Intoxication</i>	<i>Intoxication Chronic Use Withdrawal</i>
Opiates	<i>Withdrawal Chronic Use</i>	<i>Intoxication Chronic Use</i>	<i>Intoxication Chronic Use Withdrawal</i>

Sleep disorders (insomnia and parasomnia) are related to the use of other substances, such as piperazine, Hawaiian woodrose seeds, ecstasy-like drugs (MDA, MDEA, etc.) or dimethyltryptamine.

Other substances that have been anecdotally related to sleep disorders are: Phalaris Arundinacea (a plant of the grass family containing dimethyltryptamine). There is evidence of recreational use of this plant. The extract is inhaled or injected and produces a state of psychic alteration within about 10 minutes characterized by intense hallucinations and other psychedelic phenomena; Heimia salicifolia is a plant native to Mexico once used by shamans during their rituals. The infusion of this plant or the smoke arising from it produce intense euphoria associated with auditory hallucinations and reduced need for sleep; Poppy Straw is derived from a plant of the family Papaveraceae (*Papaver somniferum*) and it is widely used in medicine for its analgesic properties (opium, morphine, which is extracted). Recently, it has been inhaled or swallowed for its relaxing and euphoric effects, which also antagonize the effect of stimulants. It can induce hypersomnia type disorder; Kava-Kava, Yage, Ayahuasca, Salvia divinorum, MDPV (MethyleneDioxyPyroValerone), Ibogaine and Ivory Wave are other examples of plant-derived substances related to the onset of sleep disturbances [36].

## Conclusion

As described in this chapter, the central issue is that sleep disorders are frequently associated with the use of psychotropic substances, both legal and illegal, possibly in combination with poor sleep hygiene. On this background, we can argue that stimulants most

frequently generate insomnia during the acute effect and hypersomnia during withdrawal; vice versa, “downers” (sedative substances) most frequently cause hypersomnia as an acute effect, and insomnia during chronic use or withdrawal syndrome. Both categories increase the extent of qualitative sleep disorders, such as several parasomnias. Frequently, the use of these substances is underrated by clinicians and this fact complicates the treatment of symptomatic syndromes and exposes the patient to an increased risk of adverse effects. A screening for recent or past use / abuse of substances (including alcohol, nicotine, caffeine and prescribed drugs) is essential when investigating the history of patients who present with a sleep disorder. This is very complicated, however, because the interviewee is often reluctant to talk about an illegal phenomenon (for illicit drugs), or does not want to be subject to moral criticism from society, with the possible presence of a feeling of shame. Nonetheless, when this disturbance is identified the physician will need a specific program for treatment and relapse prevention that targets not only the treatment of sleep disorder *in se*, but also the detoxification and addiction treatment. The description of specific treatments for the use / abuse of various substances mentioned above, is beyond the central purpose of this chapter and would require discussion that is oversized for the present work. Therefore, we refer to the literature in the field of integrated therapy of substance addiction, keeping in mind that the acquisition of tools for the recognition of sleep disorders related to substance use is an essential goal for the clinician.

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