Illicit Recreational Drugs and Sleep

A systematic review covering cocaine, ecstasy, LSD and cannabis

INAUGURAL - DISSERTATION
zur
Erlangung des Medizinischen Doktorgrades
der Medizinischen Fakultät
der Albert-Ludwigs-UniversitätFreiburg i.Br.

Vorgelegt 2007
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Jahr der Promotion: 2008
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Abbreviations

CBD cannabidiol
d day
DB double-blind
DSM-IV Diagnostic and Statistical Manual of Mental Disorders, fourth edition
EA early abstinence
EEG electroencephalogram
EMG electromyogram
EOG electrooculogram
h hour
HIV human immunodeficiency virus
i.v. intravenous (route of administration)
LA late abstinence
LSD lysergic acid diethylamide
MDE methylenedioxyethamphetamine
MDEA =MDE (methylenedioxyethamphetamine)
MDMA methylenedioxymethamphetamine
min minute
NREM sleep non-rapid eye movement sleep
NS not significant
PSG polysomnography
REM sleep rapid eye movement sleep
SB single-blind
SE sleep efficiency (total sleep time divided by total time in bed)
SOL sleep onset latency
SWS slow wave sleep (stages 3 and 4 sleep)
THC tetrahydrocannabinol
TST total sleep time
WASO time awake after sleep onset
wk week
1. Introduction

1.1. Objectives of this dissertation

“Recreational drug use” is a term for a substance use pattern that has gained increasing popularity (European Monitoring Centre for Drugs and Drug Addiction, 2006). It is a pattern that is opposed to the heavy daily use of hard drugs such as heroin within a milieu, separated from society. In contrast, recreational drug users are generally well-integrated and they may belong to any social class. Typically, they pursue regular activities as students, young professionals and artists. They resort to illegal substances in social contexts such as parties, where drug effects serve as an escape from the daily routine and as a relief of stress experienced before exams or at the workplace. Also, the substances are welcome for their socializing properties and their enhancement of dancing. Typical examples of drugs used in this way are cocaine, ecstasy, LSD and marijuana, but also amphetamine, psilocybin mushrooms, ketamine and γ-hydroxybutyrate.

Illicit recreational drugs are used by an alarming proportion of adolescents and young adults. According to the 2006 Monitoring the Future survey (National Institute on Drug Abuse, 2006), prior lifetime use of any illicit drugs was reported by 48.2% of U.S. American 12th graders. Specifically, lifetime use of marijuana was reported by 42.3%, of cocaine by 8.5%, of ecstasy by 6.5%, and of LSD by 3.3%, respectively.

Provided that these frequently consumed drugs disturb sleep: then it can be assumed that a relevant proportion of the sleep problems among young adults is related to drug use. This has practical implications for attending physicians, making it necessary to recognize the contribution of illicit drug use to sleep problems in patients not diagnosed with a drug use disorder. In patients with known drug abuse or dependence, treatment of substance-induced sleep disturbances may need to be incorporated into the overall treatment plan. Accordingly, this dissertation examines the impact that illicit recreational drugs exert upon sleep, during acute or chronic administration of the agent and during the acute, subacute and chronic phases of withdrawal.

On the other hand, this dissertation also takes into consideration the opposite direction of possible interactions between illicit drug use and sleep (see Figure 1). It also addresses the question of whether poor sleepers are more likely to develop an illicit drug use disorder and whether disturbed sleep during withdrawal from illicit drugs contributes to relapse. It has been shown that sleep disturbances predict subsequent onset of alcohol abuse (Ford and Kamerow, 1989; Breslau et al., 1996) and that sleep disturbances during alcohol withdrawal constitute an important risk factor of relapse (Gillin et al., 1994b; Brower et al., 1998; Drummond et al., 1998; Gann et al., 2001). Similar correlations for illicit drug use would help to identify high-risk individuals and they might open new perspectives on preventive measures.
1.2. Background

Marquardt and Schäfer (2004) divide illicit drugs into four groups: psychostimulants, entactogens, hallucinogens and central nervous system depressants. The entactogens have an intermediate position between stimulants and hallucinogens (compare Gouzoulis-Mayfrank et al., 1996). The order of the present dissertation follows this concept, starting with cocaine (1.2.1.), followed by the entactogens 3,4-methylenedioxymethamphetamine (MDMA) and 3,4-methylenedioxy-N-ethylamphetamine (MDE; 1.2.2.), the hallucinogen D-lysergic acid diethylamide (1.2.3.) and the central nervous system depressant cannabis (1.2.4.).

1.2.1. Cocaine

1.2.1.1. History

Coca leafs have been chewed and brewed up as tea in the Andes for centuries. Cocaine was extracted from coca leafs in 1855 by Friedrich Gädecke. Its chemical structure was defined better by Albert Niemann in 1859 and later by his successor Wilhelm Lossen. Shortly afterwards, it was introduced into western medicine. In 1884, Sigmund Freud recommended cocaine for the treatment of depression. Also in 1884, Koller introduced it into ophthalmology as a surface anesthetic, and a year later it was used as a conduction anesthetic by Halsted and Hall (Marquardt and Schäfer, 2004). Its chemical structure was described by Richard Willstätter in 1898.

In the early 1980’s, the “crack epidemic” spread across the United States. Crack cocaine is the freebase alkaloid form, which can be extracted from a solution of cocaine hydrochloride with buffered ammonia using ether. Today sodium bicarbonate is the base used most frequently, and the removal of
the precipitate with ether is generally omitted. The crystals are heated, and vaporized cocaine is released (Cornish and O’Brien, 1996). Crack cocaine is rarely used as a recreational drug.

1.2.1.2. Chemical structure
Cocaine (Figure 2) is a tertiary amine and belongs to the tropane family of natural alkaloids. Its tropine-element makes it resemble atropine and scopolamine.

![Figure 2: Chemical structure of cocaine](image)

1.2.1.3. Pharmacokinetics
Cocaine hydrochloride is usually administered on the nasal mucosa by snorting, but it is also well absorbed from the oral route (e.g. coca leaf chewing) and it can be injected intravenously (i.v.). Some individuals applicate cocaine on the rectal, urethral or vaginal mucosa with the intention of improving sexual experience. Crack cocaine is smoked.

In general, snorting doses range from 20 to 200 mg, but tolerance resulting from chronic abuse may increase the dose up to 1 g. After nasal application, psychotropic effects begin within 2 to 3 minutes, stay on a peak level for about 30 to 60 minutes and disappear after approximately three hours. The plasma half-life of cocaine is 30 to 90 minutes (Berger, 2004). After smoking crack, psychotropic effects already start within 10 seconds. The rush only lasts for 5 to 10 minutes, however. Cocaine passes the blood-placenta barrier.

In the liver, cocaine is hydrolyzed by esterases to benzoylecgonine and ecgonine methyl ester. These inactive metabolites can be detected in the urine for three days, or for three weeks after chronic use (Marquardt and Schäfer, 2004).

1.2.1.4. Pharmacodynamics

*Mechanism of action*
Cocaine inhibits the presynaptic reuptake of the neurotransmitters norepinephrine, epinephrine, dopamine and serotonin.

The competitive inhibition of presynaptic dopamine transporters of axon terminals in the nucleus accumbens and the prefrontal cortex is believed to constitute the primary neurophysiologic equivalent of central cocaine effects (Vetulani, 2001).
Cocaine also exerts pronounced effects upon peripheral tissues. Depending on the expression of postsynaptic receptors, the increase in catecholamines in the synaptic junction has a variety of effects, such as, most notably, vasoconstriction in peripheral blood vessels (α1-adrenoceptors) and tachycardia due to cardiac β1-adrenoceptors. In high concentrations, cocaine acts as a local anesthetic, blocking voltage-dependent sodium channels and suppressing the propagation of the action potential. Furthermore, in high concentrations cocaine also blocks muscarinic acetylcholine receptors.

**Acute effects**

During the initial phase, cocaine produces the typical symptoms of the cocaine “kick”. It is characterized by euphoria, orgiastic feelings, motor activation, sympathomimetic arousal, increased libido and wakefulness as well as decreased appetite and thirst. Hallucinations may occur, for instance the hallucinatory perception of small creatures under the skin (“cocaine bugs”). During the subsequent phase, consumers may suffer from depressed mood, anxiety, panic attacks and paranoid delusions, accompanied by exhaustion, sleepiness and cardiovascular depression.

Life-threatening medical conditions induced by acute intoxication are mediated mainly by hypertension and vasospasm, but also by arrhythmias, increased cardiac oxygen demand, hyperthermia due to augmented metabolic rate or by serotoninerically mediated platelet aggregation. Cardiovascular complications are frequent and comprise hypertensive crises, unstable supraventricular tachycardia or ventricular tachycardia, and myocardial infarction. Similarly, vasospasms may lead to stroke, hepatic, splenic, bowel or renal infarction (Ellenhorn et al., 1997). Further potentially lethal complications include malignant hyperthermia and rhabdomyolysis. Smoked crack cocaine is associated with a broad spectrum of pulmonary damage as a consequence of vasoconstriction and toxic injury (Laposata and Mayo, 1993). Patients may present with bronchospasm, pulmonary hemorrhage and pulmonary edema up to an acute respiratory distress syndrome (ARDS). Bronchospasm may be of such intensity as to cause alveolar rupture due to increased alveolar pressure. This explains why pneumothorax, pneumomediastinum and pneumopericardium can sometimes be observed in crack cocaine abusers.

As a consequence of psychotropic drug effects, patients are at increased risk of suffering and inflicting traumatic injury, including traffic accidents and homicides. In a review by Macdonald et al. (2003), around 5% of injured drivers and even 29% of all persons who committed intentional injuries, and primarily homicides, tested positive for cocaine.

**Chronic effects**

Cocaine produces a strong psychological, but no physical dependence. The risk of dependence is even greater for crack, since drug effects occur immediately and wane again abruptly. Consequently, crack users experience marked withdrawal effects, which favors the continuation of crack consumption. Psychiatric complications of chronic cocaine abuse comprise deficits in attention and memory, sleep disturbances and irritability. The so-called cocaine-induced psychosis is a frequently observed disorder. It is estimated to affect up to two thirds of cocaine-dependent persons and it
correlates positively with dependence severity and early age of onset (Kalayasiri et al., 2006). The symptomatology resembles that of acute paranoid schizophrenia. Vasoconstriction associated with frequent snorting causes persistent rhinitis, ulcerations of the nasal mucosa up to perforation of the nasal septum and damage to the cribriform plate with resulting cerebrospinal fluid rhinorrhea. Snorting is also associated with sinusitis, which can be complicated by a brain abscess. A biventricular dilated cardiomyopathy similar to that seen in pheochromocytoma has been observed in long-term cocaine users. Chronic cocaine use also accelerates atherosclerosis (Ellenhorn et al., 1997).

Typical needle infections in intravenous cocaine users are bacterial endocarditis and human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) infection. Failure to use condoms after drug use and sex-for-drug transactions increase the risk of sexually transmitted diseases. For instance, prevalence of HIV is 2.4-fold increased among crack cocaine smokers (Edlin et al., 1994).

**Effects of prenatal exposure**

Prenatal administration of cocaine diminishes placental blood flow due to vasoconstriction in the maternal circulation, it decreases fetal cerebral blood flow and may produce direct neuronal excitotoxic injury due to catecholamines and cocaine passing the blood-placenta barrier (Ellenhorn et al., 1997). Maternal cocaine use has been shown to result in a lower birth weight, smaller head circumference and a higher risk of prematurity. Newborns often present with irritability, high-pitched crying, tremors, excessive suck, hyperalertness and difficulty to arouse. Seizures and autonomic instability are observed more frequently than in controls. Furthermore, neonates are at increased risk of infections including syphilis, hepatitis and HIV infection. A recent study suggested that cocaine exposure does not imply an increased risk of malformations (Bauer et al., 2005).

1.2.2. 3,4-Methylenedioxymethamphetamine (MDMA, “Ecstasy”) and 3,4-Methylenedioxy-N-ethylamphetamine (MDE, “Eve”)

1.2.2.1. History

3,4-Methylenedioxymethamphetamine (MDMA) was developed as an appetite suppressant. It was first synthesized by E. Merck and Company in 1912, but it was not marketed. In 1953, the U.S. Army experimented with the drug, looking for a substance that compelled the opponent’s spies to tell the truth. Shulgin and Nichols described the psychotropic effects of MDMA scientifically in 1976. Effects such as increased empathy and enhanced self-perception are often summarized as “entactogenic” properties, from Greek and Latin roots meaning “producing a touching within”. Since 1983, MDMA has been used as a recreational drug, especially at raves of the techno scene. In 1985, it was assigned status of an illicit drug with high potential for abuse by the American Food and Drug Administration. As a reaction to this, 3,4-methylenedioxy-N-ethylamphetamine (MDE, “Eve”) appeared in the drug scene as an unrestricted substitute for MDMA (Ellenhorn et al., 1997).
1.2.2.2. Chemical structure

3,4-Methylenedioxyamphetamine (MDMA; Figure 3) is a ring-substituted amphetamine derivative which is chemically related to both stimulants and hallucinogens. Like amphetamine and methamphetamine, but also like hallucinogens such as mescaline (3,4,5-trimethoxyphenethylamine) and DOM (2,5-dimethoxy-4methyl-amphetamine), it belongs to the group of arylalkanamines. 3,4-methylenedioxy-N-ethylamphetamine (MDE) is the N-ethyl-derivative of MDMA (Gouzoulis-Mayfrank et al., 1996).

![Chemical structure of 3,4-Methylenedioxyamphetamine](image)

Figure 3: Chemical structure of 3,4-Methylenedioxyamphetamine

1.2.2.3. Pharmacokinetics

MDMA is usually administered orally. Effects start after 20 to 60 minutes, reach their peak after two hours and last for 4 to 6 hours. The elimination half-life of MDMA is dose-dependent. In usual doses, it is around 8 to 9 hours (de la Torre et al., 2000). Two thirds are eliminated unchanged over the kidneys, the other third is metabolized in the liver, and active metabolites such as 3,4-Methylendioxyamphetamine (MDA) can be generated (Marquardt and Schäfer, 2004).

1.2.2.4. Pharmacodynamics

Mechanism of action

The primary effects of MDMA are believed to be mediated by the serotonin (5-hydroxy-tryptamine, 5-HT) system in the limbic system and hypothalamus. MDMA releases the transmitter directly from presynaptic vesicles, but also binds to postsynaptic 5-HT receptors, especially 5-HT-2A. Like amphetamine, MDMA releases epinephrine and dopamine, however its affinity to these transporters is low. It may also inhibit the monoamine oxidase and the presynaptic reuptake of epinephrine, dopamine and serotonin (Marquardt and Schäfer, 2004).

Acute effects

MDMA and MDE induce feelings of euphoria, intimacy, closeness to others, unconditioned love and increased self-perception. In addition to these effects which are commonly summarized by the term “entactogenic”, perceptual disturbances or even acute paranoid psychoses may occur, similar to the effects of psychedelics. Thirdly, MDMA and MDE have stimulant and arousing properties. The most common side effects are, in order of frequency, trismus (“lockjaw”), tachycardia, bruxism (teeth grinding), dry mouth, trembling and palpitations (Gouzoulis-Mayfrank et al., 1996).
Life-threatening conditions associated with MDMA intoxication are often secondary to a serotonin syndrome, an excess of serotoninergic activity in the central nervous system, but also in the periphery. This syndrome presents with malignant, severe hyperthermia, profuse sweating, muscle rigidity, tachycardia, tachypnea, rhabdomyolysis, metabolic acidosis, myoglobinuria, acute renal failure and disseminated intravascular coagulation.

Severe dehydration during prolonged dancing and physical exhaustion as well as hyponatremia and cerebral edema after abrupt and excessive drinking have been described. Furthermore, hypertensive crises with spontaneous intracranial hemorrhage may occur following MDMA ingestion (Ellenhorn et al., 1997). Acute toxic hepatitis up to acute liver failure has also been reported (Brnčić et al., 2006).

Chronic effects
There is evidence indicating that MDMA can induce permanent damage to the human brain (Gouzoulis-Mayfrank and Daumann, 2006; Lyvers, 2006). Considerable evidence of selective serotonin neurotoxicity in rodents and non-human primates has accumulated (e.g. Ricaurte et al., 1985; Ricaurte et al., 2000; Kovács et al., 2007). In humans, repeated high doses of MDMA have been reported to be associated with persisting psychiatric symptoms such as panic attacks, depression and insomnia (McCann and Ricaurte, 1991; Morgan et al., 2002) as well as cognitive changes such as deficits in verbal memory (McCann et al., 2000; Rodgers, 2000) and impairments in central executive functioning (Verkes et al., 2001).

1.2.3. D-Lysergic acid diethylamide (LSD)

1.2.3.1. History
Lysergic acid diethylamide (LSD), one of the most potent hallucinogens, was first synthesized in 1938 at Sandoz Company, Basle. Among a number of other synthetic ergot derivates which were tested for potential effects on circulation, respiration, uterine contractions and migraines, LSD did not draw any particular attention in preclinical studies. It was only in 1943, when Hofmann, one of the involved chemists, accidentally ingested a minimal amount of LSD, which led to the discovery of its psychotropic features (Aktories et al., 2005).

1.2.3.2. Chemical structure
The structure of LSD (Figure 4) resembles that of the neurotransmitter serotonin. Both substances feature an indoleethylamine nucleus.
1.2.3.3. Pharmacokinetics
LSD is usually ingested orally. Psychedelic effects can occur from a dose as low as 20 µg. Symptoms begin within 5 to 20 minutes after oral ingestion, reach their peak after 30 to 90 minutes and last for about 6 to 8 hours. The half-life of LSD is 2.5 hours. LSD is metabolized in the liver and the inactive metabolites are excreted via biliary or renal elimination (Marquardt and Schäfer, 2004).

1.2.3.4. Pharmacodynamics
Mechanism of action
LSD has a high affinity to almost all 5-HT-receptors, mostly with agonistic or partial agonistic effects. In particular, it interacts with 5-HT1A-, 2A- and 2C-receptors. Its hallucinogenic properties are attributed in particular to its strong partially agonistic effect on central 5-HT2A-receptors. The highest density of these receptors has been located in the apical dendrites of cortical pyramidal cells (Jakab and Goldman-Rakic, 1998).
LSD also acts directly on all dopamine receptor and adrenoceptor subtypes, a mechanism that is responsible for the peripheral sympathomimetic effects of this agent.

Acute effects
During the first 30 to 60 minutes after ingestion, dizziness, nausea, mydriasis, tachycardia and increased body temperature predominate. Then, sensory impressions become more intense and pseudohallucinations occur, for instance kaleidoscopic and moving patterns. High doses of LSD produce real hallucinations, which are more frequently visual than acoustic or tactile. Often, the consumer experiences synesthesias, “hearing” colors or “seeing” tones. Judgment is markedly compromised, and consumers tend to overestimate their own abilities with possibly fatal consequences. This phase may be associated with euphoric mood and uncontrolled laughter, but “horror trips” with panic attacks occur quite frequently. LSD use can lead to a neuroleptic malignant
syndrome, a life-threatening condition characterized by hyperthermia and rhabdomyolysis (Marquardt and Schäfer, 2004).

Chronic effects
LSD can have a number of long-term effects. Aside from exacerbating a preexisting psychiatric illness, it may also induce prolonged psychotic reactions, depression, flashbacks and the so-called “hallucinogen persisting perception disorder”. This disorder can occur even after a single dose, and is described by the patients as “living in a bubble under water” or “living in a purple haze”. In contrast to flashbacks, which are episodic, this perception disorder may persist stable for years (Abraham, 1983).

1.2.4. Cannabis
1.2.4.1. History
Cannabis has been cultivated in Central Asia since at least 7000 B.C. in order to make clothes and ropes. A variety of cannabis sativa that contains only a small fraction of the main psychotropic component Δ-9-tetrahydrocannabinol (Δ-9-THC) is still an important fiber in the textile industry nowadays. References to the use of cannabis for its medicinal and later, psychotropic, properties date back to at least 2000 B.C. Interestingly, in ancient India it was recommended as an analgetic in rheumatic diseases, as an appetite stimulant and as a hypnotic. It was only in 1839 that the Irish physician O’Shaughnessy introduced cannabis into Western medicine, based on his experiences in the British Army in India. In the Western world, oral ingestion of hashish for non-medicinal purposes began around 1850, whereas reports of cannabis use by smoking date back to only around 1910. The chemical structure of Δ-9-THC was first described by Maomi and Mechoulam in 1964. Marijuana has become very popular among adolescents and young adults since the “flower-power-movement” in the 1960s (Zuardi 2006).

1.2.4.2. Chemical structure
The cannabis plant contains at least 400 chemical compounds, about 60 of which are cannabinoids. Out of these, the most important is Δ-9-THC (Figure 5), to which most of its psychoactive effects are attributed. Only the (-)-enantiomer of Δ-9-THC occurs in nature (McGilveray, 2005). The non-psychoactive cannabidiol (CBD; Figure 6) and the relatively sparse Δ-8-THC are further compounds.

Figure 5: Chemical structure of Δ-9-Tetrahydrocannabinol
1.2.4.3. Pharmacokinetics

After inhalation, 15 to 50% of a marijuana cigarette’s Δ-9-THC is absorbed into systemic circulation. Psychotropic effects set in within seconds to a few minutes, reach their maximum after 30 minutes and last for 2 to 4 hours. Oral Δ-9-THC is only about 6% bioavailable. Subjective effects start after 30 to 90 minutes, reach a maximum after 2 to 3 hours and taper off within 4 to 12 hours. THC passes the blood-placenta barrier. The active 11-hydroxy-THC as well as the inactive 11-nor-9-carboxy-THC constitute the major initial metabolites of Δ-9-THC. They are generated predominantly in the liver. Since large quantities of the lipophilic THC are stored in the fatty tissues, and due to extensive enterohepatic circulation, only 30% of Δ-9-THC and its metabolites are excreted within the first week. 70% of THC are eliminated via biliary excretion and 30% undergo elimination over the kidneys as glucuronidated 11-nor-9-carboxy-THC (Aktories et al., 2005; Grotenhermen, 2003; McGilveray, 2005).

1.2.4.4. Pharmacodynamics

Mechanism of action

There are two known subtypes of cannabinoid receptors, CB1- and CB2-receptors. They belong to the family of G-protein-coupled receptors. Whereas CB2-receptors are expressed mostly on cells of the immune system, CB1-receptors are primarily located in the central nervous system, where they can also be presynaptic and hence interact with a great variety of other neurotransmitters and neuromodulators. The highest density of CB1-receptors is found in the frontal cortex, hippocampus, cerebellum and basal ganglia (Iversen, 2003). The (-)-enantiomer of Δ-9-THC is 10 to 100 times more potent than the (+)-enantiomer. According to Fride and Shohami (2002), some central effects of Δ-9-THC are not mediated exclusively by CB1-receptors, but also by 5-HT2 receptors and/or others. Cannabidiol (CBD) has only very little affinity for CB1 receptors, but it has antagonistic properties on these receptors (Petitet et al., 1998). It stimulates vanilloid VR1 receptors and inhibits the uptake and hydrolysis of anandamide, an endogenous cannabinoid (Bisogno et al., 2001). The exact mechanism of action of CBD still remains to be clarified.
Acute effects
Marijuana effects are highly variable, but often described as a feeling of mild euphoria, a “high”, peacefulness, relaxation, drowsiness, an altered time sense or a dream-like state. Tachycardia and conjunctival reddening accompany the psychological effects of marijuana.

The acute toxicity of Δ-9-THC is low. Acute psychoses lasting up to 48 hours may occur (Degenhardt et al., 2001). They are characterized by paranoia, anxiety and, occasionally, suicidal ideation. Acute panic reactions constitute a rather frequent, but generally mild psychological adverse effect, especially in inexperienced users. Consumers may set themselves and others at considerable risk due to impairment of driving performance. A recent review concluded that marijuana use increases the risk of road crashes at least by factor 2.4 (Mura et al., 2006).

Chronic effects
Marijuana smoking is associated with a fivefold greater increase of blood carboxyhemoglobin levels than smoking of tobacco, and with a three- to fourfold greater increment in the amount of tar deposited in the lower respiratory tract (Wu et al., 1988). There is an increased incidence of respiratory tract malignancy, such as cancer of the mouth, jaw, tongue, larynx and lungs (Caplan, 1991; Tashkin, 1993).

In spite of some difficulties to separate cannabis effects from a potential premorbid personality which predisposes for cannabis use, substantial evidence has accumulated to resolve the controversy over long-term psychiatric effects of cannabis use. Chronic and excessive cannabis abuse has been observed to be associated with diminished motivation and lethargy (“amotivational syndrome”; Johns, 2001). A recent meta-analysis found a pooled adjusted odds ratio of 1.4 for development of persistent psychotic symptoms (Moore et al., 2007). The risk of psychotic disorders increases dose-dependently with extent of cannabis use (Moore et al., 2007). A cohort study by Patton et al. (2002) demonstrated that teenage girls who consume cannabis on a daily basis have a five-fold greater risk of developing depression and anxiety disorders. Cognitive deficits have been observed in chronic users even after three weeks of abstinence (Pope, 2002). A recent prospective study concluded that cognitive impairments can be observed in heavy users beyond cessation, however not for more than three months (Fried et al., 2005).

Effects of prenatal exposure
Studies analyzing the effects of marijuana use during pregnancy have indicated that birth weight and length may be slightly reduced in exposed infants, but that perinatal morbidity and mortality is not increased (Zuckerman et al., 1989; Fergusson et al., 2002). A case-control study by Robison et al. (1989) which suggested that cannabis-exposed infants had a greater risk of acquiring acute myeloid leukemia during childhood was not confirmed by a recent study (Trivers et al., 2006).

Health aspects
Cannabis is supposed to have a large variety of therapeutical properties. The effectiveness of Δ-9-THC as an antiemetic in chemo- and radiotherapy-induced nausea and vomiting (Plasse, 2002), as an analgesic in rheumatoid arthritis, migraine, neuropathic pain and multiple sclerosis-related pain...
(Iskedjian et al., 2007), as a muscle relaxant against muscular spasticity and hyperreflexia in multiple sclerosis (Collin et al., 2007) and as an appetite stimulant in AIDS and cancer patients have been demonstrated (Ben Amar, 2006). However, a recent multicenter, randomized controlled trial showed no differences between cannabis extract, Δ-9-THC and placebo in the treatment of patients with cancer-related anorexia and weight loss (Strasser et al., 2006). In patients with glaucoma, cannabinoids decrease intraocular pressure, but they may also reduce apoptosis of retinal ganglion cells (Tomida et al., 2007), due to their neuroprotective (Shen and Thayer, 1998; García-Arencibia et al., 2007) and vasorelaxant properties.

Yet, the risks associated with therapeutical use of cannabinoids need to be taken into consideration. A review by Thomasius et al. (2004) showed that cannabis-based medicines lacked effectiveness or tolerability in many studies. Furthermore, the investigators stressed that young persons at risk of drug abuse are likely to interpret an approval of cannabis for medicinal purposes as evidence of an alleged lack of health hazards associated with cannabis consumption. On the whole, it was concluded that the risks outweighed the potential benefits of medicinal cannabis.
2. Materials and Methods

2.1. Search strategy

2.1.1. Electronic databases

The search was designed to comprise the five most relevant electronic databases,
- Medline (since 1966)
- Embase
- CINAHL
- PsycINFO
- Psyndex

The databases CINAHL, Medline and Psyndex were searched together, employing the research database Ovid. PsycINFO was searched using EBSCO. The database searches were concluded at the end of October 2006, so all articles until October 2006 inclusive were potentially eligible for this review.

2.1.2. Key words

In order to minimize the risk of omission of relevant articles due to a too restricted and specific search, the key terms chosen comprised the variety of terms employed in scientific literature to designate the substances and its compounds. For cannabis, “synthetic cannabinoids” and specifically “nabilone” were also included. Dronabinol is Δ-9-THC and was not added. The key words are:
- Cocaine
- Methylenedioxymethamphetamine or ecstasy or MDMA; methylenedioxyethylamphetamine or methylenedioxyethamphetamine or MDEA or MDE
- Lysergic acid diethylamide or LSD
- Cannabis or marijuana or tetrahydrocannabinol or THC or cannabidiol or synthetic cannabinoids or nabilone

Following the same rationale, no specific, closed terms such as “sleep difficulty”, “sleep disturbance” or “sleep disorder” were employed as key words. Instead, each one of the aforementioned substance names was entered into the databases in conjunction with the term
- Sleep

2.2. Study selection and data extraction

Since such an open formulation of keywords resulted in a huge number of studies obtained from the databases, the study selection was performed in two steps. The idea of the first step was, on the base of a study's title and abstract, to exclude the very obviously irrelevant studies, but in case of any doubt whatsoever, to leave the studies for the second round. Since the utmost attention was paid not to lose any potentially relevant article, this approach, although subjective with respect to the number of
studies remaining after the first step, did not produce any lack of replicability regarding the eventual inclusion of articles. The exclusion criteria were:

- Articles not in English, German, French or Portuguese
- Popular scientific articles
- An obvious foreignness to this dissertation’s questions (see chapter 1.1. and inclusion criteria below)

The shortlist obtained by this first step served as the basis for the determination if an article was included in the analyses. In order to be included, an article needed to meet the following conditions:

- Original investigation
- Investigation of the relationship between the considered drugs and sleep, either as effects of drug administration or withdrawal upon sleep (ideally in the absence of other drugs) or as the impact of sleep problems upon the propensity for drug use
- Assessment of sleep with any objective form of sleep continuity or sleep architecture measures or with subjective measures such as sleep quality, perceived sleep quantity, or dreams

In addition to the database searches, the reference lists of the eligible articles were screened for further related studies.
Details about the objectives of a study, participants, study classification, interventions, data collection, statistical methods and results were recorded in preformed Windows Excel forms.

2.3. Statistical methods

The number of studies, study quality and homogeneity were sufficient to perform meta-analyses only for cocaine withdrawal, but not for any other aspect of this review. Meta-analyses were performed according to the recommendations of the Cochrane Collaboration (Higgins and Green, 2005). They were reported according to the QUOROM statement (Moher et al., 2000).

Effect sizes and their corresponding standard errors were determined for each individual study. For the pre-post design, which comprises dependent measures, absolute mean differences were calculated. Standard deviations were estimated via pooling reported standard deviations, assuming an intraindividual correlation of $r=0.5$ between measurement points. When no standard deviations were available, the highest standard deviations (SDs) from the other studies were imputed. In those studies where there were drop-outs, the remaining subjects were assumed to be representative for the group as a whole. For the independent two-group design, absolute mean differences were determined and standard deviations were calculated via pooling the reported standard deviations.

The inverse variance-based random-effects model (DerSimonian and Laird, 1986) was used to pool results of individual studies. The heterogeneity between studies was assessed via the Chi-square test and quantified using the I-square statistics (Higgins et al., 2003). The I-square value yielded the proportion of variance explained by the heterogeneity between trials. Data analyses were conducted using the Review Manager 4.2.8 software.
3. Results

3.1. Identification of studies

3.1.1. Trial flow

The combined search of the databases Medline, CINAHL, and Psyndex yielded 165 articles for cocaine, 36 for ecstasy, 96 for LSD and 232 for cannabis. In PsycINFO, there were 106 search results for cocaine, 41 for ecstasy, 54 articles for LSD and 85 for cannabis, respectively. The EMBASE search yielded 185 articles for cocaine, 45 for ecstasy, 12 for LSD and 143 for cannabis. This adds up to a total of 1200 articles identified by the database searches (Table 1).

<table>
<thead>
<tr>
<th></th>
<th># Search results Medline, CINAHL, Psyndex</th>
<th># Search results PsycINFO</th>
<th># Search results EMBASE</th>
<th>Sum of all databases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cocaine</td>
<td>165</td>
<td>106</td>
<td>185</td>
<td>456</td>
</tr>
<tr>
<td>Ecstasy</td>
<td>36</td>
<td>41</td>
<td>45</td>
<td>122</td>
</tr>
<tr>
<td>LSD</td>
<td>96</td>
<td>54</td>
<td>12</td>
<td>162</td>
</tr>
<tr>
<td>Cannabis</td>
<td>232</td>
<td>85</td>
<td>143</td>
<td>460</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1200</td>
</tr>
</tbody>
</table>

Table 1: Total numbers of articles identified by the database searches

After the first step of study exclusion, there remained 63 potentially relevant articles for cocaine, 26 for ecstasy, 42 for LSD and 115 for cannabis. After applying the inclusion criteria, 27 papers were identified for cocaine, 8 for ecstasy, 12 for LSD and 41 for cannabis (Table 2).

<table>
<thead>
<tr>
<th></th>
<th>Search results</th>
<th>After step 1</th>
<th>After step 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cocaine</td>
<td>456</td>
<td>63</td>
<td>27</td>
</tr>
<tr>
<td>Ecstasy</td>
<td>122</td>
<td>26</td>
<td>8</td>
</tr>
<tr>
<td>LSD</td>
<td>162</td>
<td>42</td>
<td>12</td>
</tr>
<tr>
<td>Cannabis</td>
<td>460</td>
<td>115</td>
<td>41</td>
</tr>
<tr>
<td>Total</td>
<td>1200</td>
<td>246</td>
<td>88</td>
</tr>
</tbody>
</table>

Table 2: Trial flow: the numbers of articles in the process of identifying relevant studies
The database searches yielded no reviews on the sleep effects of cocaine, four reviews of ecstasy effects, which also mention sleep effects (Baylen and Rosenberg, 2006; Montoya et al., 2002; Morgan, 2000; Parrott, 2001), one review of “drugs and sleep”, which briefly cites sleep studies of LSD (Oswald, 1968), a review of therapeutical properties of cannabis which resumes some marijuana sleep studies (Hollister, 1986), and a review of sleep effects of marijuana and ethanol (Zarcone, 1973). No systematic review of sleep studies and no meta-analysis were found.

Twelve additional articles which were not identified by the electronic databases were included in the analyses. These twelve articles were not among the 1200 papers produced by the database searches. They were found when scrutinizing the reference lists of the initially identified papers. Since they constitute more than 10% of the altogether 100 articles analyzed in this dissertation, it is necessary to inquire why they were not detected by the searches. It needs to be ruled out that methodological problems contributed to this circumstance.

The studies by Hartmann (1967), Gillin et al. (1972) and Kales et al. (1972) were published as short abstracts, and therefore could not be detected by the database search. On the other hand, those articles were not included in which substance use or sleep disturbances played only a minor role so that the related terms merely appeared in the full text where they could not be identified by the electronic databases. Three studies were not registered because sleep abnormalities were regarded only as one of numerous cocaine withdrawal symptoms (Gawin and Kleber, 1986; Foltin and Fischman, 1997) or ecstasy effects (Verheyden et al., 2003). Two studies of sleep disturbances focused on the association with depression (Ford and Kamerow, 1989; Breslau et al., 1996). They did not cite other psychiatric disorders in title or abstract, since these correlations were regarded as less central. One article escaped the search because of the lack of a significant association between sleep disturbances and substance use. Therefore, other psychiatric disorders, but not drug use were mentioned in the abstract (Weissman et al., 1997).

The fact that the aforementioned nine studies were not detected by the databases does not appear to be related to a methodological limitation of the search strategy. Rather, they were inevitable for the search that was undertaken. The short abstracts would not have been identified by any key terms. In order to detect the other six studies, the database searches would have needed to combine each substance name not only with “sleep”, but also with “effects” (without “sleep”), and to include “psychiatric disorder” in conjunction with “sleep”. It is not convincing that the predefined criteria should have foreseen this necessity. At any rate, the total number of search results would have been over 30000 potentially eligible articles.

Three additional studies were identified ex post due to what appears to be a certain limitation of the chosen key terms. The study by Johnson and Breslau (2001) would have been detected with the key words “illicit drug” AND “sleep”, the paper by Vignau et al. (1997) with the conjunction “stimulant” AND “sleep” and the one by Reid and Simeon (2001) with the terms “cocaine” AND “dream”, respectively. It can be objected that at least “illicit drug” and “dream” would have constituted reasonable further key terms.
Since it was found that the articles which examine the impact of sleep disturbances upon the vulnerability to drug abuse generally do not distinguish between substance classes, they were collapsed into a separate group, even if a study was originally a search result for e.g. cocaine. Table 3 shows the total number of articles included in the analyses.

<table>
<thead>
<tr>
<th>Substance</th>
<th>Included in analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cocaine</td>
<td>28</td>
</tr>
<tr>
<td>Ecstasy</td>
<td>9</td>
</tr>
<tr>
<td>LSD</td>
<td>12</td>
</tr>
<tr>
<td>Cannabis</td>
<td>41</td>
</tr>
<tr>
<td>Impact of sleep on propensity for drug use</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 3: Total numbers of articles analyzed in this dissertation

3.1.2. Quality assessment

All eligible articles were classified by their level of evidence, following the Oxford Centre for Evidence-Based Medicine (2001). Studies which considered sleep measures only as a secondary outcome were considered separately. The results of this classification are presented in Table 4.
Most of the studies in humans have been flawed by common methodological limitations. Difficulties begin with sampling and the recruitment of participants. First of all, study samples are generally small. There are few studies that administer illicit drugs to drug-naïve subjects. In most studies, only those individuals are selected who seek treatment for substance-related problems or who are willing to reply to newspaper advertisements of a drug experiment. Studies in drug users are heterogeneous due to differences in the extent of prior use and the time elapsed since last use. Overlapping residual or chronic drug effects or abstinence symptoms may confound the results. The information upon extent of prior drug use often relies on self-reports. However, drugs obtained in the street are often impurified, and users can only estimate roughly the consumed doses. Secondly, recall bias is aggravated by the impairment of cognitive performance acutely produced by drug and alcohol consumption. And thirdly, the drug histories may also be distorted due to feelings of guilt and due to uncertainty regarding the confidentiality of their statements. Very frequently, participants are polydrug users. Here, the effects of the examined substance are difficult to separate from the effects of other agents. Furthermore, illicit drug users may present with considerable psychiatric comorbidity, which is per se often associated with sleep disturbances. Finally, it cannot be ruled out that sleep alterations observed in drug abusers have already existed prior to the onset of drug use. Objective and subjective sleep abnormalities may be part of premorbid characteristics which predispose to subsequent drug abuse.

During the course of the study, there are further common pitfalls. Even when subjects are instructed to refrain from daytime napping throughout the study, these instructions are enforced rigorously only in a minority of trials. Similarly, even when subjects are requested to abstain from alcohol and illegal drugs (in addition to the administration protocol), the participants’ compliance is not always confirmed by

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Sleep as primary outcome</th>
<th>Sleep not primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meta-analysis or systematic review of randomized controlled trials</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Randomized controlled trial; prospective cohort study with good follow-up</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Non-randomized, controlled trial</td>
<td>34</td>
<td>1</td>
</tr>
<tr>
<td>Cohort study with follow-up &lt;80%; untreated patients in randomized controlled trial</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Cross-sectional study</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>Case-control study</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Observational study</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Preclinical study</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>95</strong></td>
<td><strong>5</strong></td>
</tr>
</tbody>
</table>

Table 4: Assessment of the quality of studies analyzed in this dissertation by their level of evidence.
breath alcohol analyzers and toxicological urinalysis. Other substances that may affect the results if consumed during the study are caffeine, over-the-counter drugs and nicotine. For instance, subjects might attempt to alleviate abstinence symptoms by increased consumption of coffee or cigarette smoking.

Since these confounders are present in the majority of studies, they will not be repeated for each article in the following analyses. However, those study characteristics that were designed to reduce some these difficulties will be mentioned consistently. Also, the named confounding elements will be cited explicitly whenever they play a particularly momentous role in a certain context.

3.2. Effects of illicit recreational drugs upon sleep

3.2.1. Cocaine

3.2.1.1. Study characteristics

28 papers were included in the analyses: three animal experiments, one case report, one clinical observation, eight cross-sectional studies, two cohort studies and 13 clinical studies (see Table 5). Out of the 25 studies in humans, ten employed polysomnography (PSG) in adults and nine assessed subjective ratings of sleep. Six studies examined the effects of prenatal cocaine exposure upon sleep (see Table 6).

<table>
<thead>
<tr>
<th></th>
<th>Animal experiment</th>
<th>Case report</th>
<th>Cross-sectional study</th>
<th>Cohort study</th>
<th>Case-control study</th>
<th>Clinical trial</th>
<th>sum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cocaine</td>
<td>3</td>
<td>2</td>
<td>8</td>
<td>2</td>
<td>0</td>
<td>13</td>
<td>28</td>
</tr>
</tbody>
</table>

Table 5: Classification of the analyzed studies on cocaine and sleep

<table>
<thead>
<tr>
<th></th>
<th>PSG studies</th>
<th>Subjective effects</th>
<th>Prenatal exposure</th>
<th>Sum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cocaine</td>
<td>10</td>
<td>9</td>
<td>6</td>
<td>25</td>
</tr>
</tbody>
</table>

Table 6: Sleep studies of cocaine in humans

3.2.1.2. Preclinical studies

There are two studies which investigated the acute effects of cocaine upon behavioral state in animals, one in the rat (Hill et al., 1977; see Table 7) and the other in fetal sheep (Abrams et al.,
Furthermore, there is one experiment which examined the effects of prenatal exposure to cocaine upon outcomes in newborn piglets (Moss and Laferrière, 1998).

<table>
<thead>
<tr>
<th>Publication</th>
<th>Purpose of study</th>
<th>Subjects</th>
<th>Study design, administration protocol and outcome measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hill et al., 1977</td>
<td>sleep effects of cocaine in rat</td>
<td>20 male Sprague-Dawley rats</td>
<td>• oral or intraperitoneal administration of placebo or 6 mg/kg cocaine, separated by 7-d interval</td>
<td>• increase in SOL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• recordings for 7 h</td>
<td>• decrease in SWS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• increase in REM sleep during first half of the sleep recording</td>
<td>• decrease in REM sleep during first half of the sleep recording</td>
</tr>
<tr>
<td>Abrams et al., 1992</td>
<td>effects of cocaine on behavioral state in fetal sheep</td>
<td>6 pregnant ewes carrying singleton fetuses</td>
<td>• fetal circulation: i.v. infusion of 33 mg cocaine or placebo over 60 min, recordings 102 min prior to, during, and 102 min after infusion</td>
<td>• decrease in both REM and NREM sleep and increase in indeterminate state</td>
</tr>
<tr>
<td></td>
<td></td>
<td>last 3wk of pregnancy</td>
<td>• spectral analysis</td>
<td>• no changes in fetal blood gases</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• increase in delta and theta, decrease in beta bandwidths</td>
</tr>
<tr>
<td>Moss and Laferrière, 1998</td>
<td>prenatal cocaine exposure in piglets</td>
<td>10 pregnant Yucatan miniature sows and piglets</td>
<td>• maternal circulation: i.v. infusion of placebo or 2 mg/kg cocaine 4X/d during last five weeks of gestation, piglets evaluated at ages 3-9 d or 21-31 d</td>
<td>• less wakefulness than unexposed group (only older group)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• sleep data from initial normoxia (10 min) 1X/d for 5 d</td>
<td>• more quiet sleep (NS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• more active sleep (only younger group)</td>
</tr>
</tbody>
</table>

Table 7: Animal experiments of cocaine effects upon sleep

In the study by Hill et al. (1977), 20 male Sprague-Dawley rats were administered placebo or 6 mg/kg of cocaine hydrochloride, either as an oral intubation in distilled water or as an intraperitoneal injection dissolved in saline. Sleep electroencephalogram (EEG) recordings were obtained for seven hours. Administrations were separated by intervals of seven days. There was a significant increase in wakefulness, as evidenced by an increase in sleep onset latency (SOL) and significant decreases in total sleep time (TST) and in non-rapid eye movement (NREM) sleep. Rapid eye movement (REM) sleep was reduced only during the first half of the night, and tended to be increased compared to placebo in the second half. The effects of cocaine were more prominent after intraperitoneal injection.

The study does not contain any obvious weaknesses.

Abrams et al. (1992) studied the acute effects of cocaine on the sleep EEG in six fetal sheep at a gestational age of 128 to 135 days (last three weeks of pregnancy). Experiments started already two days after implantation of electrodes in some sheep. Saline placebo or 33.4 mg of cocaine were infused i.v. into the fetal circulation during 60 minutes on alternate experimental days in a cross-over design. Electrocorticogram (ECoG), neck electromyogram (EMG) and electrooculogram (EOG) recordings were performed 102 minutes prior to, during and 102 minutes after infusion. Samples of fetal arterial blood gases were drawn repeatedly.

Cocaine administration disrupted the typical behavioral state cyclicity normally observed in fetal sheep at that time of gestation. Both REM and NREM sleep were decreased, and an indeterminate state, which has been regarded as “wakefulness” in such fetuses, was increased. REM sleep suppression appeared to be more pronounced than the reduction in NREM sleep. There was no significant REM rebound during the 102 minutes of post-drug recording. Spectral analysis revealed increments in the
delta and theta bands, and a decrease in beta spectral amplitudes. Intermediate bandwidths were not affected. Since no changes in fetal blood gases were observed, cocaine effects were not mediated by hypoxia.

One has to bear in mind that, instead of imitating maternal cocaine use and investigating sleep EEG outcomes in the newborn, the present trial was designed merely as a study of acute cocaine effects. Complicated surgery was necessary to administer cocaine and to examine sleep in fetuses. It can be objected that two days of recovery may not have been enough time to guarantee undisturbed recordings.

In the study by Moss and Laferrière (1998), five pregnant Yucatan miniature sows received 2 mg/kg of cocaine hydrochloride i.v. four times a day from gestational day 77 until delivery, for a mean of 38 days. There was a control group of five pregnant control sows of identical gestational age. Instrumentation was performed at least two days before experiments. Piglets were evaluated starting on postnatal days 3 to 9 (younger group) or 21 to 31 (older group). According to the investigators, this would be equivalent of 1-to-2-week-old and 5-to-6-month old infants, respectively. Aside from subsequent experiments of diaphragmatic EMG activity under hypoxic conditions, sleep-wakefulness patterns were assessed during an initial period of 10 minutes of normoxia. These experiments were repeated for five days.

The older group (21 to 31 days) spent significantly less time in the awake state than unexposed controls, and there was a non-significant (NS) increase in quiet and active sleep. The increments in active sleep were the most prominent, and they achieved statistical significance in the younger group (3 to 9 days). There were substantial differences in diaphragmatic EMG activity between the exposed and non-exposed and younger and older groups. Cocaine-treated piglets had augmented diaphragmatic activity in the absence of differences in arterial blood gases or hyperventilation in the pre-hypoxic condition. The short periods of sleep state assessment (10 minutes per day) constitute the most obvious limitation of this study. A longer pre-hypoxic phase with respective recordings would have been more appropriate.

3.2.1.3. PSG studies of cocaine administration and withdrawal

Sleep effects of cocaine administration

There is only one study which explicitly examines the effects of acute cocaine administration upon polysomnographically monitored sleep in humans (Post et al., 1974). The case report by Subramanya and Ramachandran (2006) describes a sleep profile which may have been induced by chronic cocaine consumption (see Table 8). There are additional, confirmatory data upon the sleep during cocaine binges from the studies by Watson et al. (1992), Johanson et al. (1999), Pace-Schott et al. (2005a) and Morgan et al. (2006). These articles will be discussed below in the section “PSG measures during cocaine withdrawal”.
Post et al. (1974) examined the mood and sleep effects of oral cocaine administered to five moderately to severely depressed patients (ages 43 to 54). One patient was studied twice. The study design was a single-blind, within-subject placebo-controlled trial. After an adaptation night, patients spent four nights in the laboratory on placebo, followed by six nights of oral administration of cocaine in two doses (at 9 P.M. and 10 P.M.). The initial daily dose was 30 to 60 mg. It was gradually augmented to a dose of 65 to 200 mg. Afterwards, there were another three nights on placebo.

Administration of cocaine led to a significant decrease in TST and in REM sleep. Both the number and the length of REM sleep episodes were reduced, however each non-significantly. The decrease in REM sleep was dose-dependent. Upon withdrawal, there was an increase in REM sleep, constituting the so called REM rebound. These alterations of PSG measures were noteworthy in view of the fact that neither mood nor behavioral nor physiologic parameters were subtle enough to show any consistent changes over the experiment.

An apparent weakness of this study is that sleep, particularly REM sleep, is altered markedly in depressed patients. The findings may not be securely transferable to healthy individuals.

A case report by Subramanya and Ramachandran (2006) describes an HIV-positive and supposedly cocaine-dependent male, 49 years of age. The patient had been on highly active anti-retroviral therapy for about six years and had an undetectable viral load, a cluster of differentiation (CD)-4 count of more than 500/µl and no history of opportunistic infections. He presented with an eleven-month history of progressive, severe hypersomnia, sleeping continuous up to three or four days and still not waking up refreshed. Presumably, there were occasional sleep-walking episodes.

Aside from his hypersomnia, the patient’s physical exam was unremarkable. The patient had a body mass index of 21. His score on the Epworth Sleepiness Scale, a self-rating questionnaire, was the maximum value of 24. Complete blood count, liver enzymes and markers of inflammation were normal. Meningitis, encephalitis, hypothyroidism, epilepsy and iron deficiency were ruled out and

Table 8: Studies investigating the effect of cocaine upon objective measures of sleep

<table>
<thead>
<tr>
<th>Publication</th>
<th>Purpose of study</th>
<th>Subjects</th>
<th>Study design, administration protocol and outcomes</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post et al., 1974</td>
<td>oral cocaine in depressed patients</td>
<td>5 depressed patients (1 studied twice)</td>
<td>SB, non-randomized, placebo-controlled trial, PSG: 1 adaptation night, 4 placebo nights, 6 d oral administration of initially 30-60 mg/d, finally 65-200 mg/d cocaine at 9 A.M. and 10 P.M.</td>
<td>administration: decrease in TST and REM sleep</td>
</tr>
<tr>
<td>Subramanya and Ramachandran, 2006</td>
<td>case report of severe hypersomnia in a cocaine-dependent patient</td>
<td>1 cocaine-dependent patient age 49zure posive, undetectable viral load, CD4&gt;500/µl</td>
<td>case report, history, physical exam, laboratory tests of blood, cerebrospinal fluid and urine, radiograms, PSG, Multiple Sleep Latency Test</td>
<td>patient reports excessive daytime somnolence for 11 months</td>
</tr>
</tbody>
</table>
magnetic resonance imaging (MRI) of the brain was normal. However, a single photon emission computed tomography (SPECT) suggested a diffuse vasculitis or inflammation of the central nervous system. Orexin levels in the cerebrospinal fluid were within normal limits (226pg/ml). In spite of the patient's denial of having used cocaine, urine toxicology screens were positive for this agent. It is not stated why the investigators assume that he was addicted to cocaine. The patient performed the Multiple Sleep Latency Test and was submitted to a single night of PSG studies.

The patient had a TST of 348 minutes with a sleep efficiency (SE; defined as total sleeping time divided by total time in bed) of 90%. He spent 1% of his sleeping time in stage 1 sleep and 60% in stage 2 sleep. SWS percentage was relatively high with 17%, REM sleep percentage was 22%. He had 75 central and 41 obstructive hypopneas for an index of 20 events per hour. He spent less than 1% of the night with an oxygen saturation below 90%. The periodic leg movements in sleep (PLMS) index was 42 events per hour, with a periodic leg movements in sleep (PLMS) arousal index of 10. Mean SOL for the five nap opportunities of the Sleep Latency Test was very short (2.5 minutes). There were no sleep onset REM periods, i.e. no REM sleep occurring within 15 minutes of sleep onset.

The patient's sleepiness improved when he was prescribed carbidopa. Furthermore, he received the stimulant substance modafinil, and he was advised to use continuous positive airway pressure (CPAP) for the treatment of his obstructive sleep hypopneas.

According to the investigators, the patient's hypersomnia may be a result of chronic cocaine consumption. They reason that cocaine has two effects on the dopamine transporters of neuronal terminals: it inhibits the reuptake of dopamine competitively, but it also upregulates surface expression of these transporters. Hence, if the latter outweighs the former, e.g. after repeated exposure, the net effect of cocaine administration would be a decrease of dopamine at the synaptic junction, hence leading to sleepiness. This investigators regard their hypothesis as confirmed by the fact that the patient's hypersomnolence improved with carbidopa, which increases dopamine at the synapse. However, the investigators fail to monitor periodic leg movements in sleep (PLMS)-dependent arousals in order to investigate whether they were reduced by carbidopa to an extent that would explain the observed improvement in alertness.

Sleep apnea and periodic limb movements are not typically found in cocaine users and they may not necessarily be related to the cocaine use by this patient. The circumstance that the diffuse inflammation of the central nervous system may be relevant to the observed symptomatology is not considered by the investigators.

On the whole, this anecdotal report is not capable of establishing an unambiguous relationship between chronic cocaine use and sleep disturbance.

**PSG measures during cocaine withdrawal**

Eight trials have been carried out to examine polysomnographically monitored sleep during acute withdrawal from cocaine (see Table 9). Three of these lacked specificity for cocaine (Gillin et al., 1994; Thompson et al., 1995; Lukas et al., 1996). The time course of abstinence until the subacute phase was also addressed in all but two (Watson et al., 1992; Lukas et al., 1996) of these investigations. Acute cocaine withdrawal is commonly defined as the first nine or ten days after cessation of drug consumption.
<table>
<thead>
<tr>
<th>Publication</th>
<th>Purpose of study</th>
<th>Subjects</th>
<th>Study design, administration protocol and outcome measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kowatch et al., 1992</td>
<td>sleep and mood during cocaine withdrawal</td>
<td>9 cocaine-dependent subjects</td>
<td>open, non-randomized trial, 17 d abstinence, frequent PSG recordings, sleep, mood and craving questionnaires, substance abuse treatment program</td>
<td>increase in total time awake (nights 2-5), SE and SOL poor throughout experiment, decrease in stage 3% and stage 4%, increase in REM sleep% and REM density, decrease in REM sleep latency on various nights, subjective sleep quality: about &quot;same as usual&quot; throughout study, improvement in mood after 2nd day</td>
</tr>
<tr>
<td>Watson et al., 1992</td>
<td>sleep and mood during cocaine withdrawal</td>
<td>3 recreational intranasal cocaine users, ages 24-32</td>
<td>open, non-randomized trial, no inpatient admission, PSG: 1 adaptation, 1 baseline night, then administration of 1 to 1.5 g of cocaine over the following evening, three recovery nights, assessment of mood and craving</td>
<td>baseline night: normal levels, cocaine night: decrease in total REM sleep and REM density, increase in REM latency, recovery nights: increase in total REM sleep, highest measures on second recovery night</td>
</tr>
<tr>
<td>Gillin et al., 1994</td>
<td>lisuride treatment of stimulant withdrawal</td>
<td>22 dependent on cocaine, 3 amphetamines, 3 both, ages 23-48, n=6 with PSG in placebo arm</td>
<td>DB, paired, placebo-controlled trial, within 1-2 d of admission, baseline for 2-6 d, then treatment phase, administration of lisuride or placebo at PAGG at least twice a week</td>
<td>placebo group with short REM latency, reduced TST, increased REM sleep and reduced SWS, linear increase in SOL, decrease in TST from baseline over acute to subacute abstinence (NS)</td>
</tr>
<tr>
<td>Thompson et al., 1995</td>
<td>sleep during abstinence in alcoholics and stimulant abusers</td>
<td>14 stimulant abusers, mean age 33, 16 alcoholics (mean age 38)</td>
<td>open, non-randomized trial, PSG nearly every night after admission, acute withdrawal and subacute withdrawal, data collapsed for each phase in 7 stimulant abusers</td>
<td>compared to alcoholics: more stage 2% and less REM% during withdrawal, compared to normative data: during acute abstinence, total REM sleep increased, REM density decreased, during subacute abstinence, decrease in TST, SE and SWS</td>
</tr>
<tr>
<td>Lukas et al., 1996</td>
<td>buprenorphine treatment in abstinent combined cocaine and heroin abusers</td>
<td>20 male, both cocaine- and heroin-dependent subjects, mean age 33</td>
<td>open, non-randomized trial, no treatment during first 9 d, PSG recordings on days 4 and 5, then, 4 mg or 8 mg (n=10 each) buprenorphine sublingual/d, PSG recordings on days 18 and 19, treatment discontinued on day 23, no further PSG recordings</td>
<td>initial abstinence: decrease in TST and SE, increase in SOL, wakefulness's, almost no SWS, short REM sleep latency, buprenorphine treatment: improvement in SOL for both dosages, but only lower dose associated with improvements on other measures</td>
</tr>
<tr>
<td>Johanson et al., 1999</td>
<td>sleep during cocaine withdrawal</td>
<td>3 male cocaine-dependent subjects, ages 37-40</td>
<td>DB, non-randomized, controlled trial, 8-10 d abstinence, 5 d intranasal administration of placebo at 8 A.M. and 600 mg cocaine/d before 9:30pm, 15-16 d abstinence, PSG on 2-3 nights each phase, questionnaires on craving, mood and drug effects</td>
<td>controlled cocaine intake: decrease in SE, increase in SOL, decrease in REM% compared to controls, abstinence: increase in SOL, worsening; decrease in REM latency; decrease in SE from night 7 on, Multiple Sleep Latency Test: SOL decreased until day 2, sleep onset REM periods increased until day 8</td>
</tr>
<tr>
<td>Pace-Schott et al., 2005a</td>
<td>sleep over a binge-abstinence cycle in cocaine dependent subjects</td>
<td>5 cocaine-dependent subjects, mean age 36.4</td>
<td>open, non-randomized trial, 3 d abstinence, then 3 d smoked crack (mostly 600 mg/d) at 11 A.M. and 2 P.M., then 15 d abstinence, PSG recordings on 11 nights across binge-abstinence, Nightcap monitor on remaining nights, sleep, mood questionnaires each morning, cognitive tasks</td>
<td>decrease in TST and SE across binge-and-abstinence; increase in SOL and WASO%TST, decrease in REM latency across binge-and-abstinence, subjective sleep quality unchanged over abstinence, improvement in a canonical sleep index, low depression scores during all phases</td>
</tr>
<tr>
<td>Morgan et al., 2006</td>
<td>objective and subjective sleep and procedural learning during cocaine withdrawal</td>
<td>12 cocaine-dependent subjects, ages 24-49</td>
<td>DB, cross-over, controlled trial, i.v. self-administration of cocaine (mean 223 mg/d) on days 4-6 or 18-20, from 12 to 2 P.M., PSG recordings on 11 nights; Nightcap monitor worn nightly, open bedtime, subjective ratings of sleep and alertness, motor sequence task with retest in the morning and vigilance tests</td>
<td>binge: longest SOL, best performance on digit vigilance tests, acute abstinence: longest TST, shortest SOL, earliest bedtime, best SE, subacute abstinence: shortest TST, longest SOL, latest bedtime, worst SE, lowest arousal index, highest values for δ and θ range, performance on digit vigilance and procedural learning worst, subjective ratings of sleep and alertness: improvement across abstinence</td>
</tr>
</tbody>
</table>

Table 9: Studies investigating objective sleep measures during cocaine abstinence
Kowatch et al. (1992) examined sleep and mood parameters during cocaine withdrawal in nine cocaine-dependent subjects (four female; mean age 28.5). The majority binged heavily during the week before the trial, adding up to a mean total of 5.7 g of cocaine during that week. Smoked crack cocaine was the preferred route of administration in eight individuals, one injected cocaine intravenously. Participants were involved in a substance abuse treatment program and were submitted to PSG recordings. Subjects were assessed using the Hamilton Depression Scale, the Profile of Mood States and the Cocaine Craving Scale. Individuals rated their subjective sleep quality in the morning after PSG recordings. Bedtime and wake-up time were chosen individually by each subject during the first week of abstinence. The phase delay of the participants sleep cycle at admission had normalized by the second week of the trial. By the start of the last week of the study protocol, only four subjects were remaining in the facility, and only 3 completed the study. Normative values were derived from data for control subjects between 20 and 29 years (Roffwarg et al., 1985). The REM sleep percentage from these normative data was relatively low (17.5%).

When compared to the normative values, subjects had a long TST and poor sleep onset latencies and sleep efficiency during acute cocaine withdrawal. SWS percentage was low. On the other hand, REM sleep percentage, number of REM sleep periods and REM density were high and REM sleep latency short, constituting an REM rebound. These measures achieved statistical significance compared to normative values only in selected nights, and the values for SOL and SE not in any of the nights. The same sleep patterns continued during subacute withdrawal and the total mean for SOL and SE even went into the direction of poorer sleep, resembling sleep profiles of chronic insomniacs. However, univariate repeated measures analysis of variance (ANOVA) did not detect any significant differences across the abstinence period.

The investigators state that during the first three days of withdrawal, subjective sleep quality was “worse than usual” and afterwards “same as usual”. However, Figure 6 of that paper (Kowatch et al., 1992) shows that this interpretation is not entirely correct: sleep quality was slightly “worse than usual” on days 2, 3, 9 and 15 of abstinence, it was “same as usual” on days 8 and 16, and slightly “better than usual” on days 4 and 5. Subjective ratings of depression fell precipitously after the second withdrawal day, and cocaine craving declined markedly during the first 4 days. There was a significant, positive correlation between REM sleep latency and cocaine craving as well as mean Hamilton score. Yet, there is no further comment upon these correlations or upon the oddness that a shorter REM latency was associated with a lower score on the Hamilton Depression Scale.

The study contains a number of weaknesses: the high drop-out rate might have confounded the results for the later phases of abstinence. Presumably, there was no adaptation night. There was no control for the effects of the psychotherapy and the increasing familiarity with the surroundings.

In order to study the presumed similarity between cocaine and amphetamines with respect to their neuropharmacologic action, Watson et al. (1992) recruited three healthy recreational intranasal cocaine users. The individuals (ages 24 to 32) reported having used cocaine about 25 times per year for a mean of 3.5 years. Doses per session ranged from 0.75 to 2.0 g. Subjects were not seeking treatment. After an adaptation night, they spent another night in the laboratory for baseline recordings. This was followed by the self-administration of an estimated 1.0-1.5 g of cocaine in the early evening
of the subsequent day in the subjects’ natural environment. They returned to the laboratory, where they stayed that night and the three following nights. Subjects did not take any naps during the daytime. Mood and cocaine craving was assessed twice a day throughout the study. The participants’ sleep profile during baseline was compatible with that of healthy young adults. After cocaine administration, total REM sleep duration, REM sleep percentage and REM density were decreased, and REM sleep latency was increased. Yet, it is not stated whether these alterations reached statistical significance. During all three recovery nights, total amount of REM sleep was increased significantly. The highest measures were obtained on the second follow-up night. The other alterations of REM sleep measures did not reach statistical significance: REM density was increased only during the first recovery night, and REM sleep latency was decreased on the first and second night. Sleep continuity and NREM sleep measures remained unchanged.

Participants of this study were only relatively light cocaine users (25 occasions per year). Therefore, it is not surprising that sleep continuity measures did not change significantly across the study. Sample size was very small (n=3). Drug administration was not controlled, which was partly compensated by the identification of plasma cocaine levels. Also, it is not stated when subjects had last used cocaine prior to the admission to the study.

Common withdrawal symptoms among abusers of cocaine and amphetamine are depressed mood, exhaustion, anhedonia, disturbed sleep and craving. These symptoms are attributed to a state of functional dopamine depletion in the central nervous system. Gillin et al. (1994) therefore investigated whether a dopamine receptor agonist, lisuride, reduced symptoms of withdrawal from psychostimulants. The 28 study participants were seeking treatment in an inpatient facility. 22 of them had a main diagnosis of cocaine dependence, 3 of amphetamine dependence and another 3 of dependence on both of these agents. Only a current opiate dependence was a psychiatric exclusion criterion. Owing to this lack of rigid exclusion criteria, other substance use disorders as well as affective and anxiety disorders were highly prevalent among participants. The time that had elapsed since last use of psychostimulants was between 0 and 3 days (mean 1.0). The study was designed as a double-blind, paired, placebo-controlled trial. Within one or two days of admission, baseline records were obtained for 2 to 6 days. During the treatment phase, lisuride or placebo were administered four times a day, with each dose of lisuride increasing gradually from 0.2 mg initially to 1.0 mg on days 8 to 18. Days one to seven of this phase were collapsed into “early abstinence” and days 8 to 18 into “late abstinence”. Urine toxicology screens were obtained throughout the study. Sleep EEG was registered at least twice a week, and mood and craving were assessed at least three times per week. Owing to a high drop-out rate, only 21 patients provided sufficient data for statistical analysis.

An informal comparison with normative values (no reference given) revealed that the placebo group had a short TST, reduced SWS, a short REM sleep latency and increased total REM sleep. In the placebo group, there was a linear increase in TST across conditions. Presumably, the other alterations did not achieve statistical significance: SOL increased across the experiment, and during late abstinence, time awake after sleep onset (WASO) and total REM sleep duration decreased compared to baseline. The lisuride group had a significantly longer REM sleep latency and a decreased REM
sleep percentage, and there was a trend for an increase in WASO. Mood and craving ratings were not altered by the dopamine agonist.

First of all and most importantly, the study lacks specificity for cocaine. In addition to this, the comparison of lisuride to placebo was the principal outcome of this trial. As a consequence, it does not provide sufficient information upon the abstinence symptomatology per se, since there was no group of normal controls. Amount and pattern of drug administration prior to the abstinence period were not controlled for.

Thompson et al. (1995) compared sleep patterns of alcoholics and stimulant abusers during acute and subacute abstinence. 14 treatment-seeking stimulant abusers (mean age 33) were compared to a group of 16 alcoholics in an open, non-controlled trial in an inpatient facility. Nine patients used cocaine, three amphetamines, and two used both. Similar to the previously mentioned study, secondary psychiatric diagnoses were not considered as an exclusion criterion. PSG recordings of the stimulant abusers were performed nearly every night after admission. Data for days three to ten since last use of stimulants were lumped together as acute withdrawal for seven stimulant abusers, and days 11 to 14 as subacute withdrawal for the other seven. Additional data for 20 healthy, age-matched controls were taken from pre-existing records. It is not stated whether these controls were monitored for a single or several consecutive nights in the sleep laboratory.

In an informal comparison with this normative data, total REM sleep percentage was increased during acute withdrawal and REM density decreased. TST, SE and SWS were decreased during the subacute phase of abstinence. Compared to alcoholics, stimulant abusers had longer TST and spent more time in stage 2 sleep and less time in stage 1 and REM sleep, if these measures were taken as percentage of TST. Whereas TST and total REM sleep declined across the experiment for stimulant abusers, these measures changed in the opposite direction for alcoholics. Although no assessment of mood is referred to in the article, Table 2 from Thompson et al. (1995) indicates that the stimulant abusers had mean values of 6.5 and 10 on the 24-item Hamilton Depression Scale during acute and subacute withdrawal, respectively. Hence, mood ratings were below the threshold for a diagnosis of depression.

The weaknesses of this trial are similar to those of the previously mentioned one: the study results are confounded by blending together abusers of different psychostimulants. A comparison with normal controls was not initially planned in the study design. Drug consumption prior to the withdrawal period was not controlled. Psychiatric comorbidity was prevalent. In addition to that, concealed use of psychoactive agents during the experiment cannot be ruled out due to a lack of toxicological drug screens. Stimulant abusers were significantly younger than alcoholics in this study.

The sleep during withdrawal of combined cocaine- and heroin-dependent subjects was examined by Lukas et al. (1996). The patients were 20 male, otherwise healthy individuals with a mean age of 33 years. 12 of them had been detoxified from heroin by using methadone for up to two weeks, before being admitted to the inpatient facility. There, patients did not receive any medication for the first nine days. PSG recordings were obtained on days 4 and 5. In the morning of day 10, participants were administered 1mg of buprenorphine as a sublingual tablet. Buprenorphine is an opioid analgesic,
acting as a partial agonist on µ- and as an antagonist on κ-receptors. It has been approved for opioid substitution in heroin addiction. The dose of 1 mg was subsequently augmented to 4 mg per day in ten patients, and to 8 mg per day in the other ten. PSG tracings were repeated after eight days of treatment. The medication was discontinued from day 23 of the trial on, but no further sleep recordings were performed.

At the end of the first week of abstinence, the combined cocaine- and heroin-dependent patients had a long SOL, increased wakefulness as a percentage of time in bed, decreased TST and reduced SWS percentage. These measures differed by at least three standard deviations from normative values (Williams et al., 1974; Kowatch et al., 1992). SE was only 70 to 72%. SWS was suppressed almost entirely. REM sleep latency was short.

After eight days of treatment, the group receiving the lower dose of buprenorphine showed improvements in all of these measures. The higher dose of buprenorphine only decreased SOL, whereas the other measures did not differ significantly from the initial recordings.

Since all of the participants were also opiate-dependent, the sleep effects of heroin withdrawal superposed those of cocaine abstinence. Hence, the results are only of suggestive value for this dissertation. With respect to the results of the buprenorphine treatment, it needs to be held in mind that patients were not blinded, and that there was no control group receiving placebo.

Three healthy cocaine-dependent males (ages 37 to 40) participated in the double-blind, non-randomized, placebo-controlled trial by Johanson et al. (1999). They were monitored continuously for 28 to 31 days in an inpatient facility. They were not allowed to receive any visitors. After an initial phase of adaptation and controlled abstinence from cocaine (8 to 10 days), there was a period of controlled cocaine intake (5 days) which allowed to study the acute effects of cocaine upon sleep and provided a well-defined and equal basis for the subsequent withdrawal phase (14 to 16 days). In the mornings, “placebo” which actually contained 4 mg cocaine per 70 kg body weight was self-administered intranasally. Six sessions of 100 mg cocaine per 70 kg body weight each started at 7 P.M. with 30-minute intervals. However, the participants were used to smoking crack cocaine as the primary route of administration in their natural environment. Questionnaires concerning mood, craving and subjective drug effects were filled out and PSG recordings and the Multiple Sleep Latency Test were performed during all three phases. PSG measures were compared to those from age-matched controls (no reference given).

During the simulated binge, SOL was markedly elevated, and SE and REM sleep percentage were decreased. During the subsequent withdrawal, SOL remained increased compared with controls, and REM sleep latency was reduced. SE was decreased significantly only from night 7 on. SOL on the Sleep Latency Test was shorter than controls during acute abstinence, but longer than controls during subacute withdrawal. Sleep onset REM periods were frequent during acute abstinence, but disappeared by the end of the study.

The study was well conducted. The small sample size, the intranasal route of administration of cocaine hydrochloride instead of smoked crack cocaine and the lack of quantification of NREM sleep measures constitute the most prominent limitations of this study.
Pace-Schott et al. (2005a) examined changes in sleep over a controlled binge-abstinence period in cocaine-dependent subjects. Five volunteers (ages 30 to 41), four males and one female, who were not seeking treatment, participated in this open clinical trial. They remained 22 days in an inpatient facility: three days of initial abstinence, followed by three days of smoked cocaine use and 15 days of abstinence. Smoking sessions were at 11 A.M. and 2 P.M. on each of the three binge days, and subjects usually opted to smoke the full amount of 300 mg cocaine per session. PSG tracings were obtained on nights 2, 4 to 6, 9, 11 to 13, 16, 20 and 21. The remaining nights, participants wore the Nightcap sleep monitor. In addition to this, subjective sleep quality was assessed each morning, using the Sleep Quality Questionnaire and one question of each the Beck Depression Inventory and the General Symptom Checklist. Subjects also completed a battery of cognitive tasks twice a day.

TST and SE declined significantly across the binge-abstinence cycle. SOL, when calculated to the first 10 minutes of sleep, and WASO as a percentage of TST increased across the study. However, these measures only retained large, non-significant effect sizes when regression analyses were performed across abstinence-only. There were no significant alterations of the percentage of SWS. REM sleep latency decreased across the binge-abstinence cycle. REM sleep as a percentage of TST did not change over the assessment period. In contrast to the deterioration of objective sleep measures, the subjective assessment of sleep, as measured by the composite index of the sleep items from the Beck Depression Inventory and General Symptom Checklist, improved significantly over abstinence-only. Also, subjective SOL was greater than objective SOL during binge, and this relationship was reversed during abstinence. The trends were preserved if the one frequently napping subject was excluded from the analyses. Cognitive performance deteriorated over the binge-abstinence cycle (Pace-Schott et al., 2005b). The Beck Depression Inventory scores remained well below the threshold for depression during all phases of the trial.

The study contains only a few weaknesses. There was no control group, which could have eliminated effects of the increasing familiarity with the study protocol and environment. PSG recordings were not obtained every night.

Morgan et al. (2006) addressed the discrepancy between objective and subjective measures of sleep observed in previous studies of cocaine withdrawal. Twelve out of fourteen crack cocaine-dependent volunteers (ages 24-49; two female) completed this double-blind, cross-over controlled trial. Participants were not seeking treatment. They had no dependence on any further substance except for nicotine and no diagnosis of a sleep disorder. Toxicological screens were positive for cocaine and negative for other drugs of abuse. The inpatient facility allowed for controlled cigarette smoking, but strictly prohibited daytime napping. Cocaine was self-administered between 12 and 2 P.M. during the safety session on day 0, and on each of days either 4 to 6 or 18 to 20, whereas placebo was given on the other three-day sequence. The maximum available dose per day was 384 mg per 70kg body weight, and the mean daily consumption was 223 mg per 70kg. PSG recordings were obtained on nights 1, 3 to 8, 10, 12, 15 and 17 to 22. The Nightcap sleep monitor was worn nightly. Individuals were free to choose their bedtime between 9:30 P.M. and 7:45 A.M. Subjective measures of sleep and alertness were obtained every morning, employing the Sleep Quality Questionnaire (Pace-Schott et al., 2005a). A simple reaction time task and a test that assessed digit vigilance by presenting a
sequence of numbers were performed in the afternoon. A motor sequence task in the evening with a retest the next morning was carried out to assess sleep-dependent procedural learning. Early and late binge groups showed no differences in any of the main sleep or cognitive measures. Sleep continuity parameters varied significantly across conditions: TST was low compared to normative data on abstinence nights 4 to 6, however decreased even more and reached lowest values on abstinence nights 14 to 17. SOL, although long with respect to normative data, was shortest on nights 1 to 3 and 4 to 6, and longest at binge and nights 10 to 13 and 14 to 17. In the same way, sleep efficiency was best during acute abstinence (nights 4 to 6) and reached lowest values on nights 14 to 17. Furthermore, bedtime was latest on nights 14 to 17. The participants’ performance on the digit vigilance and motor sequence task deteriorated across abstinence. On the other hand, the arousal index was lowest during later abstinence (nights 14 to 17) and highest during acute abstinence (days 4 to 6), and spectral analysis showed highest values for the delta and theta range at binge and during subacute abstinence (nights 10 to 17). Subjective ratings of overall sleep quality, depth of sleep, feeling well-rested in the morning and mental alertness improved significantly across abstinence. There were no changes over time in WASO, SWS and simple reaction time. Data for REM sleep measures are not presented in this paper.

The study was conducted very well.

3.2.1.4. Meta-analysis of objective sleep measures during acute and subacute cocaine withdrawal

Meta-analyses were performed to compare objective sleep measures during acute withdrawal from cocaine with those during subacute withdrawal. The initial hypothesis to be tested was that sleep quality deteriorates with continued abstinence. The first nine (8 to 10) days of cocaine withdrawal are considered as acute withdrawal, or early abstinence (EA). The studies furnish data up to withdrawal day 19, and this phase is regarded as subacute withdrawal, or late abstinence (LA).

There are six studies that provide PSG data for both of these phases (Kowatch et al., 1992; Gillin et al., 1994; Thompson et al., 1995; Johanson et al., 1999; Pace-Schott et al., 2005a; Morgan et al., 2006). These are non-randomized, controlled trials. Hence, the meta-analyses are of observational data. Outcome measures were TST, SOL, SE, SWS as a percentage of TST, REM sleep latency and REM sleep percentage. Not all studies provided data upon all measures. The study by Gillin et al. (1995) did not provide any data on SE and on REM sleep latency, the one by Johanson et al. (1999) not on TST and SWS percentage, the one by Pace-Schott et al. (2005a) not on SWS percentage as well as REM percentage and Morgan et al. (2006) not on REM sleep measures, respectively.

In the study by Kowatch et al. (1992), the EA means and the SDs (with an assumed $r=0.5$) were pooled from seven values, and the LA means and SDs (with an assumed $r=0.5$) were pooled from three values. For SE, the highest SDs from the other studies were imputed. The study by Johanson et al. (1999) did not provide any SDs for the reported values. Therefore, the highest SDs from the other studies were imputed. In the study by Morgan et al. (2006), the EA means and the SDs were pooled from three values, and the LA means and SDs from two values, respectively. In the study by Thompson et al. (1995), the groups for EA and LA consist of different individuals. The standard error
of the effect size was calculated correspondingly. No study provided data on the standard deviations (SDs) for SWS percentage of TST. Therefore, conservative SDs of 5% were imputed, i.e. 95% of the data points were assumed to be in the range of ±10% of mean values.

The pooled mean values for acute withdrawal do not take into consideration available data from two further PSG studies (Watson et al., 1992; Lukas et al., 1996). These two studies do not evaluate subacute withdrawal. Their participants differ considerably from those of the other studies. Individuals in the study by Watson et al. (1992) were light, recreational cocaine users, who were examined after a single dose of cocaine. As expected, they did not experience a withdrawal syndrome. The study by Lukas et al. (1996) was conducted exclusively in subjects who were also dependent on heroin.

The pooled mean TST was 366 minutes during acute cocaine withdrawal. This value is remarkably low. A recent study revealed that in chronic insomniacs the mean TST before treatment was 359 minutes (Jacobs et al., 2004). However, during subacute withdrawal, the weighted mean TST of the cocaine-dependent subjects declined even further to a mean of 344 minutes. The pooled TST mean difference between early and late abstinence hence yielded 22 minutes, favoring early abstinence (see Figure 7). This difference was statistically significant. The 95% confidence interval was from 5 to 39 minutes (P=0.01). No considerable heterogeneity was found (Chi²=3.89, P=0.42; I²=0%).

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Mean difference</th>
<th>Mean difference (random) 95% CI</th>
<th>Weight</th>
<th>Mean difference (random) 95% CI</th>
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</thead>
<tbody>
<tr>
<td>Gil 1994</td>
<td>16.0000 (29.5900)</td>
<td>8.54  16.00 (-41.82, 73.82)</td>
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<td></td>
</tr>
<tr>
<td>Thompson 1995</td>
<td>49.0000 (24.1100)</td>
<td>12.79 49.00 (-4.25, 90.25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pace-Schott 2005</td>
<td>20.1000 (37.8700)</td>
<td>5.19  20.10 (-54.12, 94.32)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morgan 2006</td>
<td>11.6700 (10.5600)</td>
<td>61.91 11.67 (-9.61, 33.15)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 108.00 22.05 [-5.15, 38.53]

Test for heterogeneity: Chi²=3.89, df=4 (P=0.42), I²=0%
Test for overall effect: Z=2.95 (P=0.01)

Figure 7: Forest plot of the TST mean difference between early abstinence (EA) and late abstinence (LA); standard errors of mean difference are given in () brackets

The study by Morgan et al. (2006) had the smallest standard errors and by far the greatest weight in the pooled data. The pooled mean values for SOL and SE were determined by this single study at 63% and 76%, respectively. That means this study affected the results of the meta-analyses up to three times more than all the other studies combined.

However, in this study individuals were free to choose their bedtimes. Patients went to bed only when they felt tired enough, which was fairly late at night, and when they woke up early in the morning, they got out of bed and set their own lights-on time. This means that persons had individual values for total time in bed. Although this design has the advantage of being a more naturalistic model of cocaine...
withdrawal, the comparison of the values for SOL and SE with those from the other studies in this meta-analysis is difficult. Since subjects were rigorously prevented from taking daytime naps, TST values from this study are reliable. It was therefore decided to run the meta-analyses for SOL and SE without the study by Morgan et al. (2006).

The pooled mean difference for sleep onset latency between EA and LA failed to achieve statistical significance, if the study by Morgan et al. (2006) was not considered (see Figure 8). During acute withdrawal, the pooled mean SOL was 25 minutes, and during subacute withdrawal it increased to 33 minutes. No considerable heterogeneity was found (Chi²=1.37; P=0.85; I²=0%).

<table>
<thead>
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<th>Study or sub-category</th>
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<th>Weight</th>
<th>Mean difference (random)</th>
</tr>
</thead>
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<td>Kovatch 1992</td>
<td>~1.1600 (13.1600)</td>
<td>~15.80</td>
<td>~18.16 [-7.33, 43.65]</td>
</tr>
<tr>
<td>Gilin 1994</td>
<td>.97000 (94.0000)</td>
<td>2.36</td>
<td>27.00 [-39.70, 93.70]</td>
</tr>
<tr>
<td>Thompson 1995</td>
<td>8.0000 (8.0400)</td>
<td>42.33</td>
<td>8.00 [-7.75, 23.76]</td>
</tr>
<tr>
<td>Johansen 1999</td>
<td>4.0000 (48.1300)</td>
<td>1.18</td>
<td>4.00 [-9.33, 98.33]</td>
</tr>
<tr>
<td>Pacc-Schott 2005</td>
<td>2.0000 (8.4500)</td>
<td>38.32</td>
<td>2.30 [-14.25, 18.85]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>100.00</td>
<td>7.82</td>
<td>-2.42 [26.08]</td>
</tr>
</tbody>
</table>

Figure 8: Forest plot of the pooled SOL mean difference between EA and LA; standard errors of the mean difference are given in () brackets.

The weighted mean SE during acute cocaine withdrawal was 86%, and it subsequently decreased to 82%. The pooled mean difference in SE between EA and LA was 4.2% (P=0.01; see Figure 9), with a confidence interval of 0.92 to 7.43. No considerable heterogeneity was found (Chi²=0.49; P=0.97; I²=0%).
The pooled mean SWS percentage was 6% during both acute and subacute withdrawal (no considerable heterogeneity, $I^2=1\%$). REM sleep latency was markedly short during both phases of abstinence, but no significant changes were found between early and late abstinence. The weighted mean REM latency was only 59 minutes during EA and decreased further to 55 minutes during LA ($P=0.37$; no heterogeneity $I^2=0\%$). In a meta-analysis of PSG studies in depressed patients, the mean REM sleep latency was a comparable 58 minutes (Hudson et al., 1992). As demonstrated above (chapter 3.2.1.3.), depressed mood was not observed in the PSG studies of cocaine withdrawal. This means that the short REM latencies were not accounted for exclusively by depression. When analyzing the data for REM sleep percentage, which were provided by four studies, considerable heterogeneity was detected ($I^2=68\%>50\%$). Parenthetically, no changes across abstinence were found.

3.2.1.5. Studies measuring subjective effects of cocaine upon sleep

*Subjective sleep effects of cocaine administration*

There are two studies (Smith et al., 1989; Williamson et al., 1997) which specifically address the adverse effects of cocaine intake and mention sleep (see Table 10). Additional information about the subjective sleep effects of acute cocaine administration can be obtained from the studies by Foltin and Fischman (1997) and by Dudish-Poulsen and Hatsukami (2000). These two articles will be discussed below in the section “Subjective sleep quality during acute and subacute withdrawal from cocaine”, since they focus on cocaine abstinence.
Table 10: Studies investigating adverse effects of cocaine intake with respect to subjective sleep quality

Smith et al. (1989) present the results of questionnaires administered to 28 adolescent heavy cocaine users (ages 15 to 17 years; 21 male) who had been in a drug rehabilitation program for a month. 96% of the subjects were polydrug users. The investigators do not provide any information on characteristics of the questionnaires employed. Apparently, they obtained a detailed drug, family and social history and asked about frequent problems and adverse effects of cocaine consumption. 18% reported sleep disturbance as a side effect of cocaine use. The only other side effects mentioned are paranoia (46%) and tolerance to cocaine (25%).

The limitations of this article are obvious. The cited percentages are difficult to interpret without any further details on the questionnaires. The severity and clinical relevance of the described symptoms are not clear. All participants were treatment seekers, and their reports may have been confounded by recall bias and the difficulty to separate cocaine effects from those of other substances.

Williamson et al. (1997) studied the adverse effects of cocaine use, but also of ecstasy and amphetamine. 158 drug users were questioned about drug use patterns and side effects by so called “privileged access interviewers” who developed contacts with users in the community. 94 had used intranasal cocaine hydrochloride within the past year, and 82 ecstasy, respectively.

About 7% reported severe sleep disturbances as a side effect of cocaine consumption. Adverse effects did not differ significantly with respect to the different routes of cocaine administration. Remarkably, sleep problems were even more frequent for ecstasy: 13% of ecstasy users mentioned severe sleep disturbances, and the mean severity score for trouble sleeping was higher than for any other adverse effect. It achieved a mean score of 1.3 on a Likert scale from 0 to 3. Sleep disturbances were most frequent and most severe in association with amphetamine, with as many as 40% of users experiencing severe problems. 88% of users reported some sleep disturbances for an overall severity score of 2.0.

Aside from polydrug usage and the possibility of recall bias, this study does not contain any obvious biases.
Prevalence of sleep disturbances during cocaine withdrawal

Two cross-sectional studies have investigated the prevalence of sleep disturbances during abstinence from cocaine (Brower et al., 1988; Cottler et al., 1993; see Table 11).

<table>
<thead>
<tr>
<th>Publication</th>
<th>Purpose of study</th>
<th>Subjects</th>
<th>Study design, administration protocol and outcome measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brower et al., 1988</td>
<td>validity of DSM-III-R criteria for cocaine withdrawal</td>
<td>75 patients (3 female) with cocaine abuse within previous 30 d; mean age 33</td>
<td>survey; questionnaire offered to veterans seeking treatment for psychiatric problems of any kind; list of 15 symptoms to be marked either as yes or no, for last attempt of abstinence from cocaine</td>
<td>83% reported some withdrawal symptoms; 71% sleep disturbance; 69% fatigue; 33% increased dreaming</td>
</tr>
<tr>
<td>Cottler et al., 1993</td>
<td>validity of proposed DSM-IV criteria for cocaine withdrawal</td>
<td>196 and 412 regular drug users (47% and 29% female); mean age 32; 533 cocaine users</td>
<td>survey; participants from new treatment admissions or identified by street outreach workers; individuals who had lifetime consumption of at least 6 times considered cocaine users; checklist of abstinence symptoms</td>
<td>34% reported trouble sleeping as withdrawal symptom; 37% feeling tired; symptoms reported more frequently by combined opiate-cocaine users (NS); feeling tired more frequent in female cocaine users; earlier onset of cocaine use associated with greater incidence of abstinence effects</td>
</tr>
</tbody>
</table>

Table 11: Surveys examining the prevalence of sleep disturbances during cocaine withdrawal

In order to check the validity of the Diagnostic and Statistical Manual of Mental Disorders (DSM)-III-R criteria for cocaine withdrawal, Brower et al. (1988) surveyed 75 patients who admitted cocaine abuse within the past month. Patients had a mean age of 33. Only three were female. Subjects were selected out of 1115 consecutive veterans seeking treatment for psychiatric problems of any kind. The questionnaire examined extent of past cocaine use, asked whether a subject had ever experienced withdrawal symptoms, and it contained a list of 15 possible withdrawal symptoms. Patients placed a mark in either the “yes” or “no” column. 83% of the patients with recent cocaine abuse reported some withdrawal symptoms. These reported a significantly higher amount of cocaine consumed within the past month compared to the “no withdrawal group” (20 g versus 8 g). Groups did not differ significantly with respect to abuse of other substances. 71% of all cocaine users reported sleep disturbance during withdrawal, which constituted the second most frequent symptom after depression. 69% experienced fatigue (third most frequent), and 33% increased dreaming. The questionnaires did not assess the severity of symptoms. Hence, the relevance of the findings is not entirely clear. Moreover, the lack of control for psychiatric comorbidity and the retrospective assessment of withdrawal symptoms (recall bias) may constitute further confounding elements.

Cottler et al. (1993) designed a similar survey five years later in view of the planned fourth version of the DSM. The samples for this study originated from two different studies. 196 subjects (mean age 31.9; 47% female) were recruited from new treatment admissions for substance use disorders in a field trial funded by the American Psychiatric Association. 80% had ever used cocaine. 412 individuals (mean age also 31.9%; 29% female) were recruited by street outreach workers from the project...
“Efforts to Reduce the Spread of AIDS”. 88% of all drug users from both studies, i.e. 533 subjects, had used cocaine at least six times during their lifetimes. These were included in the analyses. 315 of them did not inject opiates concomitantly, and this group was compared to the mixed cocaine and opiate group. All items of a list of possible abstinence symptoms were read out individually to all participants, who gave a “yes” or “no” answer whether they had experienced this symptom.

Trouble sleeping was cited by 34% of all cocaine users and fatigue by 37%, respectively. They were among the five most frequently reported abstinence symptoms, after depression, restlessness or irritability and trouble concentrating. Fatigue was correlated positively with female gender, and both symptoms were negatively correlated with age of onset of cocaine use, i.e. they were reported more frequently by individuals who had started cocaine use at an earlier age. The combined cocaine and opiate users experienced these symptoms more frequently, but this finding did not achieve statistical significance.

The study was well conducted, but it also relies on the accuracy of the participants’ observations and memory.

The differences between the two cross-sectional studies with regard to the prevalence of sleep disturbance (71% versus 34%) and fatigue can probably attributed to the fact that apparently, extent of cocaine use was much greater in the first study. Cocaine users from by Brower et al. (1988) used a mean of almost 18 g cocaine within the prior month. In the study by Cottler et al. (1993), all individuals with a lifetime use of cocaine on six occasions were included in the analyses. Both studies are in agreement that sleep disturbance and fatigue are among the most frequently reported withdrawal symptoms.

Subjective sleep quality during acute and subacute withdrawal from cocaine

The time course of cocaine withdrawal has been investigated by a number of studies. As reported above, the trials by Kowatch et al. (1992), Pace-Schott et al. (2005a) and Morgan et al. (2006) demonstrated that subjective sleep quality remained unchanged or improved across abstinence. Overall, the participants of these studies did not complain of severe sleep disturbances. There are five more studies which explicitly address the subjective effects of withdrawal from cocaine and mention sleep (Gawin and Kleber, 1986; Weddington et al., 1990; Foltin and Fischman, 1997; Coffey et al., 2000; Dudish-Poulsen and Hatsukami, 2000; see Table 12). Gawin and Kleber (1986) found a considerable subjective improvement of initially disturbed sleep. In the remaining studies, only mild sleep problems and no changes between acute and subacute abstinence were observed. On the whole, all of the existing data upon subjective sleep quality are incompatible with the deterioration of objective sleep measures during subacute withdrawal reported above (chapter 3.2.1.4.). This discrepancy will be addressed in the Discussion (chapter 4.1.1.1.).
Withdrawal, which usually lasted for five days after cocaine binges. They defined the conclusion of the first phase as three days and nights of sleep normalization.

Interview Schedule or an abbreviated version. The investigators had pre-defined criteria whether patients were also interviewed on the basis of the National Institute of Mental Health's Diagnostic symptoms were monitored in these interviews. Within one week of enrolling in the treatment program, individual psychotherapy up to three times a week and participated weekly group sessions. Abstinence attempts to remain abstinent. Mean age was 28.6 years, and 27% were female. Subjects received hypersomnia, irritability and increased appetite were typical symptoms of the initial phase of cocaine withdrawal, which usually lasted for five days after cocaine binges. They defined the conclusion of the first phase as three days and nights of sleep normalization.

<table>
<thead>
<tr>
<th>Publication</th>
<th>Purpose of study</th>
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<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gawin and Kleber, 1986</td>
<td>time course of cocaine withdrawal and differentiation from psychiatric comorbidity</td>
<td>30 chronic cocaine abusers • mean age 29 • 14 subjects without another axis-1 diagnosis</td>
<td>• clinical observation • outpatient study • within one week, assessment of drug history and of psychiatric comorbidity based on the Diagnostic Interview Schedule • psychotherapy • ratings of mood, craving, withdrawal symptoms</td>
<td>• phase 1 (after binge, lasting 9 h-4 d): extreme dysphoria, insomnia, then increasing desire to sleep, exhaustion, hypersomnolence with intermittent awakenings • phase 2, 1 (lasting 1-5 d): normalized mood and sleep • phase 2, 2 (1-10wk): strong craving, anxiety, irritability • phase 3 (indefinite): euthymic mood, episodic craving</td>
</tr>
<tr>
<td>Weddington et al., 1990</td>
<td>time course of cocaine withdrawal</td>
<td>12 cocaine-dependent males • mean age 28 • 10 control subjects with mean age 32</td>
<td>• open, non-randomized, controlled trial • 28-d inpatient study • DSM-III-R diagnoses evaluated in semi-structured interview • Saint Mary's Hospital Sleep Questionnaire • mood and craving questionnaires • psychotherapy</td>
<td>• cocaine subjects with greater difficulty falling asleep throughout study • both groups with improvements in all sleep measures over time (except difficulty falling asleep) • cocaine subjects improved more in clear-headedness upon arising</td>
</tr>
<tr>
<td>Foltin and Fischman, 1997</td>
<td>symptoms of acute withdrawal from cocaine</td>
<td>9 male, almost daily crack cocaine users • not seeking treatment • ages 28-41</td>
<td>• open, non-randomized trial • inpatient study • self-administration of a mean total of 0.9 g crack cocaine over 2 d of one week, sessions at 12 and 4 P.M. • self-administration of a mean total of 1.3 g over three days of the other week • exposure to cocaine-related cues • St. Mary’s Hospital Sleep Questionnaire • assessment of subjective effects</td>
<td>• no alterations of subjective sleep, no complaints of sleep disturbances • only subtle changes in mood</td>
</tr>
<tr>
<td>Coffey et al., 2000</td>
<td>time course of cocaine withdrawal</td>
<td>24 cocaine-dependent subjects (10 female) • mean age 35</td>
<td>• open, non-randomized clinical trial • 28-d outpatient study • Saint Mary’s Hospital Sleep Questionnaire • questionnaires on withdrawal symptoms</td>
<td>• no changes over time in any subjective sleep parameter • improvement in other withdrawal symptoms such as depression • abstainers and relapers did not differ on any measure</td>
</tr>
<tr>
<td>Dudish-Poulsen and Hatsukami, 2000</td>
<td>symptoms of acute withdrawal from cocaine</td>
<td>12 frequent crack cocaine abusers (8 male) • not seeking treatment • ages 21-45</td>
<td>• SB, placebo-controlled study • inpatient study • 1 baseline day, 4 experimental days • on these, 7 deliveries of 0.40 mg/kg smoked crack cocaine in the morning; deliveries of 0.07 mg/kg smoked crack as “placebo” • sleep and dream questionnaire, assessment of abstinence effects</td>
<td>• subjects got to sleep easier after 0.40 mg/kg dose of cocaine compared to baseline • no differences among conditions with regard to sleep quality awakening following sleep, amount or quality of dreams</td>
</tr>
</tbody>
</table>

Table 12: Studies investigating the symptomatology and time course of cocaine withdrawal

Gawin and Kleber (1986) observed 30 consecutive outpatient chronic cocaine users during their attempts to remain abstinent. Mean age was 28.6 years, and 27% were female. Subjects received individual psychotherapy up to three times a week and participated weekly group sessions. Abstinence symptoms were monitored in these interviews. Within one week of enrolling in the treatment program, patients were also interviewed on the basis of the National Institute of Mental Health’s Diagnostic Interview Schedule or an abbreviated version. The investigators had pre-defined criteria whether independent psychiatric diagnoses could be applied. They postulated a priori that depression, hypersomnia, irritability and increased appetite were typical symptoms of the initial phase of cocaine withdrawal, which usually lasted for five days after cocaine binges. They defined the conclusion of the first phase as three days and nights of sleep normalization.
Based on their observations, Gawin and Kleber developed a tri-phasic model of cocaine abstinence. Phase 1, also called “crash” (9 hours to 4 days), is characterized by dysphoria, irritability, and insomnia, followed by exhaustion and hypersomnia. Cocaine craving diminishes gradually during this period. The second phase, also designated as “withdrawal”, lasts up to two months. Mood and sleep normalize. Cocaine craving fluctuates substantially, accompanied by anhedonia, anxiety and irritability. The risk of relapse is high. Afterwards, the patient’s affective state is euthymic, and craving is only triggered episodically by cocaine-related cues. This third phase is of indefinite duration, and is called “extinction”. A similar time course was observed in patients with additional psychiatric diagnoses.

The study is merely descriptive, and abstinence symptoms were not obtained in a standardized or quantitative manner. 16 patients had another axis-1 diagnosis, and 20 out of the 30 participants were treated with psychotropic medication. Extent and pattern of cocaine use varied considerably among subjects. A methodological weakness is the aforementioned anticipation of a cocaine “crash”, which was a priori assumed to be associated with sleep disturbance. The end of this phase had even been defined by the disappearance of sleep problems. Since the investigators already started out from this fixed model before the trial, the study itself does not verify the time course of sleep disturbances during abstinence from cocaine. On the other hand, the investigators’ definition of the first and second phase of cocaine withdrawal underlines the outstanding role of sleep disturbances.

Weddington et al. (1990) investigated the cessation symptoms of 12 cocaine-dependent males (mean age 28.1) in a closed inpatient facility over a period of 28 days. Last cocaine use had been within 48 hours prior to entering the study. Daily urine toxicologies confirmed abstinence. Patients had weekly sessions with a psychiatrist and an addiction counselor. 10 additional healthy subjects (mean age 32; presumably all male) with no substance use disorder except for nicotine dependence served as a control group. The Saint Mary’s Hospital Sleep Questionnaire was administered daily in addition to mood and craving ratings.

Cocaine subjects had greater trouble falling asleep throughout the study compared to controls. There were no other significant differences in subjective sleep measures between groups. Both groups’ ratings of all sleep items except for “difficulty falling asleep” improved over time, and the improvement of “clear-headedness upon arising” was greater for cocaine subjects. Mood and craving ratings improved linearly across abstinence.

Since a similar improvement of sleep measures was observed in both groups, it appears to be related to factors such as an increasing familiarity to the experimental surroundings, and hence not a function of continued abstinence. Cessation of cocaine use was not shown to have a considerable impact upon subjective sleep, since cocaine addicts differed from healthy controls only in one item. Psychiatric comorbidity was frequent and may have confounded the study’s results. The last administration of cocaine prior to abstinence was not standardized.

The effects of only the acute phase of cocaine withdrawal were examined by Foltin and Fischman (1997). Nine male, almost daily crack cocaine users (ages 26 to 41) participated in an open, non-controlled trial. They were not seeking treatment. The limitations of an inpatient study were addressed
by exposing subjects to cocaine-related cues. Each day, participants did not know whether they were actually going to receive cocaine after exposure to the cues. On two consecutive days of one week and on three days of the other, subjects were free to self-administer a maximum of 12 doses of 50 mg crack cocaine per day, distributed over two sessions starting at noon and 4 P.M. Three individuals started with the two-day condition. Two patients with extraordinary cardiovascular responses to cocaine only received 25 mg per dose. Participants opted to use a mean total of 0.93 g of crack cocaine over the two-day condition and 1.34 g over the three days. Drug effects and craving were assessed on visual analog scales. Each morning, subjects filled out the Saint Mary's Hospital Sleep Questionnaire.

It is stated that there were no significant changes in subjective assessments of sleep, and that, on the whole, no sleep problems were mentioned by the participants. However, the investigators do not provide the exact data concerning the sleep questionnaire. Furthermore, cocaine abstinence produced only subtle changes in mood ratings.

There is only limited information about the extent of cocaine use in these subjects. It is not clear whether participants met DSM-IV criteria for cocaine dependence. The mean weekly amount of money subjects spent on cocaine prior to withdrawal ($130) was lower than in other studies of cocaine withdrawal ($310 to $500 in Pace-Schott et al. (2005a) and Morgan et al. (2006)). The lower extent of previous cocaine consumption might explain the relatively mild withdrawal symptom severity.

The 28-day study by Coffey et al (2000) was completed only by 24 of the initially 82 cocaine-dependent outpatients. Mean age of completers was 35.4 years, 10 of them were female, and 12 were also alcohol-dependent. Last cocaine use had been within 48 hours prior to inclusion. Breathalyzer values to rule out alcohol intoxication and urine drug screens covering a variety of illicit drugs besides cocaine were collected once every five days. Questionnaires concerning withdrawal symptoms and mood as well as the Saint Mary’s Hospital Sleep Questionnaire were completed on six occasions across the study. The data for days 2 and 5 of abstinence were lumped together as the first time block, days 7 and 14 as the second, and days 21 and 28 as the third time block, respectively.

There were no significant changes in any of the subjective sleep parameters across the study. The item “insomnia” from the withdrawal questionnaire showed a non-significant improvement with continued abstinence. The exact data from the sleep questionnaire are not given. Sleep problems were mild already during the acute phase. There was a linear decline in depression, anxiety, anger and craving across the study period. The investigators report “increases in cognitive skills” in the abstract (Coffey et al., 2000), however this statement only refers to a decline in subjective ratings of the item “difficulty concentrating”. Cocaine-only abusers did not differ on any measure compared to the combined cocaine and alcohol abusers. Interestingly, a comparison with the data from the drop-outs revealed no differences between study completers and non-completers. This was also true for a comparison between abstainers and those who relapsed during the study, but afterwards completed the 28-day period on a subsequent attempt. This means that in this study the intensity of cessation symptomatology was not correlated with the risk of relapse.

Since urine specimens were obtained only every five days, it cannot be ruled out that some of the completers actually relapsed during the last few days of the trial. This could have blurred actual
differences between the early and late time blocks. Also, registration of alcohol relapse without massive intoxication depended on self-reports. A more frequent collection of data might have revealed fluctuations of symptom intensity.

Dudish-Poulsen and Hatsukami (2000) examined acute cocaine abstinence in a single-blind, randomized controlled trial. 12 frequent crack cocaine users (ages 21 to 45; 4 female), who were not seeking treatment, stayed in an inpatient facility for seven days. After the day of admission and a subsequent adaptation day, participants self-administered seven deliveries of 0.07 or 0.40 mg/kg crack cocaine in the morning of four experimental days. The lower dosage served as a “placebo”. The order of experimental days was randomized. Mood ratings, abstinence symptoms and reaction time were registered upon awakening and several times in the afternoon, and participants completed the Leeds Sleep Questionnaire and a dream questionnaire each morning.

Subjects got to sleep easier after the 0.40 mg/kg dose of crack cocaine compared to baseline, whereas the lower “placebo” dose resulted in non-significant, intermediate values on this item. There were no further differences across conditions with respect to the other items of the Leeds Sleep Questionnaire. These items are “overall sleep quality”, “awakening following sleep” and “behavior following sleep”. Amount and quality of dreams did not change significantly. Since the exact data are not provided, it remains unclear if there were any non-significant trends. Increased ratings of craving, anxiety and uncertainty were reported after each delivery of the “active” dose size and up to 30 minutes after the seventh dose.

The greater ease in getting to sleep after smoking cocaine may be explained, to some degree, by habituation to the sleep environment. However, experimental days were randomized and the higher dose was more effective, albeit non-significantly, than “placebo”. It can be hypothesized that the sleep of chronic cocaine users may benefit from the consumption of a moderate dose of cocaine in the morning, since this “substitution” alleviates withdrawal symptoms. The “placebo” contained a certain amount of cocaine (about 35 mg daily total), and the higher dose was low (about 200 mg daily total) compared to the volunteers’ habitual daily dose (2.3 g). Hence, a single-day exposure to a moderate dose may not have been enough to elicit abstinence effects, all the more considering that instead of true abstinence, participants still received a low dose of crack cocaine during “withdrawal”. This inadequate drug administration protocol may have been responsible for the absence of relevant withdrawal symptoms.

3.2.1.6. Sleep effects of prenatal cocaine exposure

There are six studies that examined the sleep of infants exposed to cocaine antenatally (see Table 13). An important confounding element of these studies is that, with the exception of the trial by Scher et al. (2000), there is no adjustment for covariates such as socioeconomic status, prenatal care, co-use of alcohol, tobacco and other drugs and birth weight. Therefore, it is impossible to differentiate whether the observed sleep abnormalities are correlated with prenatal cocaine exposure or whether they are a function of the other variables.
A short abstract by Lebedun (1987) reports the results of PSG tracings registered in 11 infants who had been exposed to cocaine during pregnancy. The study also examined the sleep of nine normal controls and of seven infants born to mothers who used methadone. The recordings were performed for 60 minutes at one week postpartum and again at one, three and six months of age.

The cocaine-exposed infants had sleep patterns suggestive of a more disrupted and aroused sleep compared to the control group.

There are important limitations to this paper. There is no information given on the amount of cocaine used during pregnancy and on demographical characteristics of the mothers. No statistical analyses were performed.

Table 13: Studies investigating the sleep of infants with prenatal exposure to cocaine
Legido et al. (1992) studied sleep EEG patterns in 35 consecutive cocaine-exposed infants and compared them with those of 51 healthy, age-matched siblings of sudden infant death victims. Mean estimated gestational age was 38.3 weeks, and mean conceptional age was 42.7 weeks. 16 of the cocaine-dependent mothers were polydrug users, and 74.3% used cocaine during all trimesters. EEG and EOG recordings were obtained for 30 to 60 minutes at some time between 8 A.M. and 4 P.M. The main finding was a significantly higher percentage of exposed infants with mature, continuous SWS and well-formed sleep spindles, among infants with a conceptional age of not more than 45 weeks. It was not correlated with the duration of drug exposure or with polydrug usage. The interpretation of this observed hypermaturity and the relevance for later development are not clear. There were no significant differences between cocaine-exposed infants and the comparison group with respect to the presence of apneas, excessive sharp EEG transients, background abnormalities or dysmaturity. An increased prevalence of clinical-versus-EEG sleep state discordance among exposed infants failed to achieve statistical significance (P=0.08). In six exposed infants, only active sleep was recorded during the registration period.

Like the previously described article, this study lacks a quantitative measurement of drug consumption. Furthermore, it is doubtful whether the siblings of sudden infant death victims constitute an adequate control group, since they have been shown to present altered sleep EEG patterns themselves (Harper et al., 1981; Harper et al., 1983).

DiPietro et al. (1995) examined behavioral state and responses to auditory stimuli in 14 cocaine-exposed neonates (six female) at a mean of two days after birth. 14 unexposed infants served as normal controls. The mothers’ demographic data were similar in both groups. However, more than one third of cocaine-using mothers did not access any prenatal care. 80% smoked tobacco and 70% used alcohol during pregnancy. All control mothers received prenatal care, and only one mother used tobacco or alcohol, respectively. Cocaine-exposed newborns had a lower birth weight than controls. The infants’ responses to repeated presentations of a rattle were registered according to the Neonatal Behavioral Assessment Scale (Brazelton, 1984). Heart rate and vagal tone were assessed. Sleep state was defined by a bedside observer according to the Neonatal Behavioral Assessment Scale. The mean total observation period was 40 minutes.

Compared to normal controls, cocaine-exposed neonates showed more state changes, shorter sleep periods, and spent less time asleep and more time in a transitional, drowsy state. There was a trend for an increase in wakefulness. More cocaine-exposed infants cried during the recording. The exposed infants’ startling responses to auditory stimuli declined only after significantly more presentations of the rattle. Sleep state definition by a bedside observer is less reliable than PSG recordings. As the study by Legido et al. (1992) indicates, cocaine-exposed infants might have an increased clinical-versus-EEG sleep state discordance. This would augment the inaccuracy of the sleep state definition by a bedside observer.

Gingras et al. (1995) compared the sleep profiles of 15 cocaine-exposed neonates with those of 10 controls. Toxicological urinalyses and substance use histories were obtained at birth. Between three
and seven days after birth, infants underwent twelve-hour overnight pneumocardiogram recordings. Wakefulness, active and quiet sleep were coded on the basis of regularity of heart rate, regularity, duration and amplitude of respirations as well as artifacts on the heart rate channel. There were numerous significant differences between the groups of exposed and non-exposed newborns. Mothers in the exposed group enrolled for prenatal care later in their pregnancy and had less prenatal visits. Abuse of nicotine, ethanol, marijuana and antidepressants was more prevalent. The exposed neonates had a smaller birth weight and lower one-minute Apgar scores. TST was reduced significantly in the exposed group, and total time awake was increased. More arousals during active sleep were observed in the exposed group. Not reaching statistical significance, active sleep was increased and quiet sleep (which corresponds to NREM sleep) decreased.

The amount of indeterminate sleep cannot be measured accurately by pneumocardiogram recordings. As the study by Regalado et al. (1995; see below) suggests, indeterminate sleep might be increased in cocaine-exposed infants. It is not clear whether the observations in the present study are valid, since EEG recordings were lacking.

The sleep of 17 cocaine-exposed neonates (two weeks of age) was compared with that of 14 control infants in the study by Regalado et al. (1995). No EEG recordings were employed. A bedside observer registered eye and body movements during a four-hour period. The infants’ respiratory movements were recorded with the help of a piezoelectric transducer. The substance use histories obtained at the time of the recordings were confirmed by toxicological urinalysis at delivery and a radioimmunoassay of the mothers’ hair. Frequent cocaine use was defined as more often than once a week. Neonates with a gestational exposure to cocaine spent less time in active sleep and more time in indeterminate sleep than controls. Quiet sleep was not affected. These findings remained significant when controlling for alcohol use. Tobacco use and maternal age were not regarded as covariates since they were not correlated significantly with behavioral state alterations (P<0.10) in this study. Interestingly, less of those mothers considered frequent cocaine users by the above-cited criterion used cocaine during the third trimester, and less had a urinalysis positive for cocaine at delivery. This might explain the remarkable finding that “infrequent” cocaine use had a larger effect on active and indeterminate sleep than “frequent” use. Also, this surprising result needs to be interpreted in view of the fact that “frequency of use” definition does not account for differences in the amount of cocaine used on each occasion, and hence does not distinguish between binge and casual use.

The aforementioned disadvantages of a bedside observer (compare DiPietro et al., 1995) also apply to this study. As reported in the study by Scher et al. (2000), second trimester use of nicotine is negatively correlated with active sleep at birth. Third trimester cigarette smoking, but even more importantly second trimester nicotine use is positively correlated with the amount of time neonates spend in indeterminate sleep. In the study by Regalado et al. (1995), cocaine users smoked significantly more cigarettes during all trimesters compared to control mothers. During the second trimester, they smoked a weekly mean of 71 cigarettes compared to 11 cigarettes by mothers from the control group. Tobacco use would have needed to be treated as a covariate. According to Scher et al. (2000), all of the differences between the two groups of this study could be explained by the differences in tobacco use during the second and third trimester.
Scher et al. (2000) designed a cohort study which compared 37 infants with gestational cocaine exposure with 34 control neonates. They were submitted to PSG recordings for 120 minutes one day post-partum and again at one year of age. A total of 57 infants (i.e. more than 80% of the original sample) were available at follow-up. Mothers were selected if they used at least one line of powder cocaine per day or any crack during the first trimester. Toxicological urinalyses and substance use histories were obtained at the end of each trimester. A stepwise regression analysis was performed, entering sociodemographic characteristics, birth weight, and maternal use of alcohol, nicotine, marijuana and other illicit drugs as covariates.

Second-trimester exposure to cocaine or crack was found to predict a reduction in $\delta$ spectral power at birth. Third-trimester exposure was correlated with a decrease in $\delta$ and $\theta$ power at one year. No other significant correlations were found for cocaine, namely no differences in sleep stage percentages. Prenatal marijuana exposure was associated with increased $\theta$ spectral power and decreased $\alpha$ at birth and increased arousals during active sleep and decreased $\beta$ power at one year of age. Nicotine exposure, especially during the second trimester, considerably altered sleep at birth. Active and quiet sleep were decreased and indeterminate sleep, body movements during active and quiet sleep and arousals during quiet sleep were increased. Second-trimester alcohol exposure was positively correlated with wakefulness at birth and with total body movements during active and quiet sleep at birth.

The study does not contain any obvious biases.

### 3.2.1.7. Overview over effects of cocaine upon sleep

Animal experiments furnish evidence of the stimulant effects of cocaine administration. There is an increase in wakefulness, and both NREM and REM sleep are decreased (see Table 8).

In humans, acute administration of cocaine also increases wakefulness and decreases total sleep, particularly REM sleep.

During acute withdrawal from cocaine, wakefulness is increased, as expressed by augmented SOL and WASO. TST and SE are reduced. SWS as a percentage of TST and REM sleep latency are decreased as well. Sleep continuity measures such as TST and SE deteriorate even further during subacute cocaine withdrawal. During this phase, SWS percentage remains low and REM sleep latency continues to be short.

Surveys show that sleep disturbance is a common adverse effect of cocaine use, and that it constitutes one of the most frequent symptoms of cocaine withdrawal. Daytime somnolence and increased dreaming are further cessation symptoms. Subjective sleep quality remains unchanged or improves with during subacute withdrawal.

Studies that examined the sleep of infants with gestational exposure to cocaine have demonstrated significant alterations compared to normal controls. Yet, there is conflicting evidence with respect to the pattern of alterations.
### Cocaine

<table>
<thead>
<tr>
<th></th>
<th>Acute administration</th>
<th>Acute abstinence</th>
<th>Subacute abstinence</th>
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<td>Total time awake</td>
<td>▲</td>
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<tr>
<td>TST</td>
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</tbody>
</table>

Table 14: Overview over the effects of cocaine upon sleep; ▲▼ arrows indicate findings only from preclinical studies; ↑↓ arrows indicate studies in humans; - indicates no change; boxes left in blank if data not sufficient or conflicting evidence.

### 3.2.2. 3,4-Methylenedioxymethamphetamine (MDMA; “Ecstasy”) and 3,4-Methylenedioxy-N-ethylamphetamine (MDE; “Eve”)

#### 3.2.2.1. Study characteristics

Nine studies were eligible for analysis: one animal experiment, one case report, five cross-sectional studies and two clinical studies (Table 15). Out of the eight studies in humans, three articles measured PSG variables as outcome data and five subjective effects (Table 16).

<table>
<thead>
<tr>
<th></th>
<th>Preclinical study</th>
<th>Case report</th>
<th>Cross-sectional study</th>
<th>Cohort study</th>
<th>Case-control study</th>
<th>Clinical study</th>
<th>Sum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entactogens</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>9</td>
</tr>
</tbody>
</table>

Table 15: Classification of the analyzed studies on MDMA/MDE and sleep

<table>
<thead>
<tr>
<th></th>
<th>PSG study</th>
<th>Subjective effects</th>
<th>Sum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entactogens</td>
<td>3</td>
<td>5</td>
<td>8</td>
</tr>
</tbody>
</table>

Table 16: Sleep studies of MDMA/MDE in humans
3.2.2.2. Preclinical studies

There is one preclinical study that investigated the effect of acute MDMA administration upon behavioral state (see Table 17).

<table>
<thead>
<tr>
<th>Publication</th>
<th>Purpose of study</th>
<th>Subjects</th>
<th>Study design, administration protocol and outcome measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balogh et al., 2004</td>
<td>effects of MDMA on motor activity and vigilance in drug-naive rats and rats previously exposed to MDMA</td>
<td>66 male Dark Agouti rats, age 6 weeks</td>
<td>randomized, placebo-controlled study rats from groups 3+4 exposed to a single intraperitoneal dose of 15 mg/kg MDMA 21 d before trial groups 1+2 (n=21 each) received placebo on day 1 of trial, groups 2+4 received 15 mg/kg MDMA, groups 1+3 saline EEG and EMG recordings for groups 1+2 on days 1,3,5,14 and 28, for groups 3+4 on day 1</td>
<td>drug-naïve rats: increase in wakefulness decrease in light and deep SWS decrease in REM, increase REM sleep latency circadian rhythms shifted by 8-15 h on the day of the treatment and still disturbed on day 28 rats previously exposed to MDMA: similar effects, but of shorter duration SOL shorter than in drug-naïve rats</td>
</tr>
</tbody>
</table>

Table 17: Available data on the acute effects of MDMA upon sleep in rats

Balogh et al. (2004) compared the effects of MDMA in drug-naïve rats with those in rats who had a single previous exposure to this substance (see Table 17). 66 male Dark Agouti rats, 6 weeks of age, were divided into four groups in order to have a placebo group both in the naïve and exposed contingents. The latter groups, which were smaller (n=12), received a single dose of 15 mg/kg MDMA intraperitoneally 21 days before the trial, constituting the previous exposure. The future naïve rats received placebo. On the first day of the trial, both naïve and exposed rats were administered 15 mg/kg MDMA intraperitoneally, and each group was controlled by a placebo group. EEG and EMG recordings were taken on days 1, 3, 5, 14 and 28 for the unexposed animals, and only on the first day for the previously exposed ones.

MDMA produced the following significant effects in the drug-naïve rats, compared to placebo: an increase in wakefulness during the first seven hours, a decrease in light SWS during the first four hours, a decrease of deep SWS in hours 2 to 7, and an increase in REM latency as well as a decrease in REM sleep in hours 2 to 11 after administration. Circadian amplitudes were reduced for various parameters on day 5, and circadian rhythms continued to be disturbed significantly for wakefulness and deep SWS on day 28. In previously exposed rats, the effects upon EEG measures were similar. However, the effects upon all sleep parameters had a shorter duration. Also, SOL was shorter compared to the drug-naïve rats.

In addition to elucidating the acute effects of MDMA administration upon sleep, the present study also furnishes evidence of longer-term alterations of the sleep-wake cycle. One apparent weakness of this study is that continuous recordings over the first few days after drug administration would have shed more light upon the subacute effects of MDMA. There were still significant changes in SWS and REM sleep on day 5, which are difficult to interpret without this additional information.

3.2.2.3. PSG studies of MDMA/MDE intake

The only PSG investigation on acute effects of entactogens was conducted with MDE (see Table 18).
The acute effects of MDE upon sleep were investigated by Gouzoulis et al. (1992) in order to find evidence whether this substance produces distinct EEG patterns which distinguish it from comparable pharmacological classes such as amphetamines and hallucinogens. Six young healthy volunteers were studied in a double-blind, randomized, cross-over, controlled manner. After an adaptation night, 140 mg of MDE or placebo were administered orally, immediately before “lights off”, and this protocol was alternated two to six weeks afterwards.

MDE produced a number of significant alterations in PSG measures: all subjects awoke within one to two hours of drug intake and stayed awake for at least another 2.5 hours. Hence, there was an increase in WASO, a decrease in TST and a decrease in SE. The fact that SOL was not affected may be explained by the fact that the drug was administered only immediately prior to going to bed. The stimulant effects of MDE were more prominent in the first half of the night. Stage 2 sleep was decreased. There were no significant effects upon stage 1 sleep or upon SWS. However, after MDE administration individuals spent a mean of 7.5% of the second half of the night in stage 4 sleep, compared to only 2.9% on placebo. This high mean percentage is even more remarkable in view of the fact that it was accounted for by the sleep patterns of three volunteers only, whereas the others either did not fall asleep again after the initial awakening (n=1) or only had some light sleep at the end of the night (n=2). In the aforementioned three subjects, sleep stage patterns appear to have shifted from the first half of the night to the second. REM sleep was suppressed completely during the entire night in five of the six subjects. The sixth participant had a single short period of REM sleep during his first sleep cycle, apparently before the substance had started to act fully. REM density was reduced in this subject. After ingestion of MDE, one individual experienced a psychotic state for three hours. On the whole, the study’s main finding was a remarkable similarity of MDE to amphetamines with relation to sleep EEG effects.

The study does not contain any obvious biases.

There are two trials which investigated persistent PSG alterations in abstinent heavy ecstasy users (see Table 19). They were performed by the same study group (Allen et al., 1993 and McCann et al., 2000) and were intended to furnish evidence of MDMA neurotoxicity in humans.
The first study (Allen et al., 1993) compared 23 young, experienced ecstasy users (consumption on >25 occasions) with 22 control subjects with no prior history of MDMA use. Participants were asked not to take any psychoactive substances for two weeks prior to the trial. No intervention was made. After an adaptation night, subjects simply spent one night in the laboratory for PSG recordings. MDMA subjects had significantly less stage 2 sleep, which was accompanied by reduced total NREM sleeping time and reduced TST. Not reaching statistical significance, WASO was slightly increased, and the mean total amount of SWS was increased (87 minutes compared to 73 minutes). Since TST was decreased, the percentage of SWS out of TST was even more striking: 23% in MDMA subjects compared to 18% in controls. REM latency was reduced (60 minutes compared to 75 minutes), but this difference did not reach statistical significance either. No data were provided on phasic activity of REM sleep.

There are some weaknesses to this study. Only one night was examined. Aside from that, there is a lack of information about the previous pattern of MDMA exposure. On the one hand, it is not stated when each individual had last used ecstasy, which could be anywhere between two weeks before and in the remote past. This could have produced heterogeneity of the study group, since it is very well possible that there are residual effects of ecstasy two weeks after use which do not constitute persistent neurodegeneration. On the other hand, the total amount of past ecstasy use is not accounted for, and neither is the age at the start of ecstasy use, which may be related to a differential vulnerability to neurotoxic agents.

The results of the other study (McCann et al., 2000) were not published. They were only mentioned in the investigators’ review about serotonin neurotoxicity. As a consequence, there is no information on the number of subjects and the design of the study.

It is stated that MDMA subjects had significantly increased TST, SE and SWS.

A critical analysis is not possible in view of the lack of data. However, the reported findings are incompatible with the sleep complaints commonly reported by heavy ecstasy users (see chapter 3.2.2.4.).

<table>
<thead>
<tr>
<th>Publication</th>
<th>Purpose of study</th>
<th>Subjects</th>
<th>Study design and outcome measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allen et al., 1993</td>
<td>persistent sleep effects of heavy MDMA use</td>
<td>23 heavy MDMA users and 22 control subjects: age 18-40</td>
<td>cross-sectional study: no drug administered; PSG: 1 adaptation night and 1 night for analysis</td>
<td>MDMA subjects with less TST, less NREM time, less stage 2 sleep; mean total SWS increased and REM latency decreased (both NS)</td>
</tr>
<tr>
<td>McCann et al., 2000</td>
<td>review on MDMA neurotoxicity, short abstract on sleep study</td>
<td>no detailed information</td>
<td>(cross-sectional study): no detailed information</td>
<td>MDMA subjects with increased TST, SE and SWS</td>
</tr>
</tbody>
</table>

Table 19: Studies investigating PSG characteristics of heavy ecstasy users
3.2.2.4. Studies assessing subjective effects of ecstasy upon sleep

**Short-term effects of MDMA upon sleep**

The study by Huxster et al. (2006) examined the acute and subacute subjective effects of ecstasy ingestion (see Table 20). There is additional information on the short-term effects of ecstasy in the study by Verheyden et al. (2003), which will be analyzed in the subsequent section (“Long-term effects of ecstasy upon sleep”).

<table>
<thead>
<tr>
<th>Publication</th>
<th>Purpose of study</th>
<th>Subjects</th>
<th>Study design and outcome measures</th>
<th>Results</th>
</tr>
</thead>
</table>
| Huxster et al., 2006 | subacute effects of MDMA | *20 male and 18 female regular MDMA users*  
*ages 18-29* | *open, non-randomized, controlled study*  
*participants opted to use MDMA (n=20) or abstain (n=18) for 9-d period*  
*baseline assessment with questionnaires on psychopathology and drug use*  
*on following 8 d at 6-8 P.M. assessment of ten items, among them “restless sleep”* | *group differences with respect to restless sleep at baseline*  
*restless sleep increased for 48 h after MDMA ingestion*  
*number of MDMA tablets consumed positively correlated with restless sleep on day 2* |

Table 20: Available data on the acute and subacute sleep effects of MDMA upon subjective sleep quality

The study by Huxster et al. (2006) controlled for differences in psychopathology among ecstasy users compared to normal individuals, since the control group consisted of MDMA users as well. 38 young, regular users, who had not used ecstasy for at least five days, participated in this open, non-randomized, controlled trial. After a baseline assessment of personality, psychopathology and history of drug use, subjects were free to choose to either use MDMA (n=20) or abstain from it (n=18) during a nine-day assessment period. In the evenings of the remaining days, participants gave telephone responses upon a number of rating scale items, among them “restless sleep”.

There were significant group differences between abstainers and users. The latter presented with greater lifetime use of ecstasy and with an elevated score of restless sleep at baseline. After drug ingestion, users had significantly higher scores for the ratings of “restless sleep” on the following 2 days compared to abstainers, even when controlling for the aforementioned covariates. On the third day, the score was still elevated, yet not significantly. In addition to this relationship, there was a positive correlation between number of MDMA tablets consumed and restless sleep on the first day afterwards.

The authors conclude, however, that these subacute effects are relatively modest in comparison with the long-term effects of heavy ecstasy use. In fact, although the subacute effects of MDMA were the primary outcome measures, the baseline assessment gave additional evidence of a correlation between lifetime ecstasy consumption and chronically disturbed sleep, of course with no deducible causality. There are no biases in this paper.

**Long-term effects of ecstasy upon sleep**

Four studies have examined the long-term subjective sleep quality in heavy ecstasy users (Parrott et al., 2000; Dughiero et al., 2001; Verheyden et al., 2003; Soar et al., 2004; see Table 21). Since three of them are surveys and the fourth is a case report, none of them is able to discriminate whether sleep...
disturbances are a consequence of MDMA use or a predisposing trait for subsequent drug consumption.

<table>
<thead>
<tr>
<th>Publication</th>
<th>Purpose of study</th>
<th>Subjects</th>
<th>Study design and data collection</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parrott et al., 2000</td>
<td>psychopathology of ecstasy users</td>
<td>• 12 heavy ecstasy users, 16 light users and 22 non-ecstasy user controls (mean age 21)</td>
<td>• survey questionnaires on drug use, personality and Symptom Checklist</td>
<td>• heavy MDMA users: higher score on &quot;restless sleep&quot; compared to controls</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• light MDMA users: intermediate scores (NS)</td>
</tr>
<tr>
<td>Dughiero et al., 2001</td>
<td>psychopathology of ecstasy users</td>
<td>• 43 MDMA users, mean age 20, 77 control subjects, 45 of them entirely drug-free (mean age 18)</td>
<td>• survey questionnaires on personality, drug use and Symptom Checklist</td>
<td>• MDMA subjects with higher scores on sleep disturbances scale, also compared to the subgroup of drug-free controls</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• no differences between experimenters and abusers</td>
</tr>
<tr>
<td>Verheyden et al., 2003</td>
<td>acute, subacute and long-term effects of ecstasy use</td>
<td>• 430 regular MDMA users (45% female), mean age 25</td>
<td>• survey questionnaires on drug use and ecstasy effects</td>
<td>• 9% with trouble sleeping 24 h after use</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• 34% with trouble sleeping 24-48 h after use</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• 21% with chronic sleep disturbance</td>
</tr>
<tr>
<td>Soar et al., 2004</td>
<td>persistence of MDMA-induced psychiatric problems after abstinence</td>
<td>• 1 Caucasian male, age 26, family history of anxiety and depression, 750 MDMA tablets</td>
<td>• case report the patient’s history, thorough neuropsychiatric examination</td>
<td>• extremely high pathology with severe sleeping problems, persisting for 7 years after last use of MDMA</td>
</tr>
</tbody>
</table>

Table 21: Studies examining subjective sleep quality in heavy ecstasy users

Parrott et al. (2000) divided the participants of their study into heavy (30 to 1000 occasions; n=12) and light (1 to 20 occasions; n=16) ecstasy users as well as non-ecstasy-user controls (n=22). Mean age was about 21 years. The study was designed as a survey, administering questionnaires on personality and past drug use to volunteers from a small town in Ireland with an active ecstasy subculture. Participants also filled out the Symptom Checklist-90 (SCL-90), a self-rating scale that includes the item “restless, disturbed sleep”.

Among MDMA users, use of amphetamine, LSD and cocaine was more prevalent than in the control group. According to the investigators, heavy ecstasy users had significantly higher scores on the “disturbed sleep” item compared with controls, whereas light users had an intermediate, non-significant score. Heavy users also had elevated scores on the somatization, obsessionality, sensitivity, anxiety, hostility, phobic anxiety, paranoid ideation, psychoticism and poor appetite subscales.

Yet, the data given by the investigators do not confirm their statement on disturbed sleep: no statistical significance is apparent for the dimensions “insomnia”, “early waking” or “restless sleep”. Hence, the statistical significance remains unclear. Aside from that, recent drug consumption is not accounted for by this study. This means that acute or subacute effects may have superposed the long-term consequences of ecstasy use. Furthermore, significant differences between groups with relation to co-use of other substances were identified. Hence, the impact of other drugs upon sleep may have confounded the results.
The psychopathological characteristics of ecstasy users were also examined in the survey by Dughiero et al. (2001). 43 ecstasy users (mean age 20) were divided into light and heavy users. The cut-off was 27.5 tablets lifetime consumption. However, the numbers of subjects in each group are not given. They were compared with 77 control subjects (mean age 18) with no history of MDMA use, 45 of which were entirely drug-free. Participants completed questionnaires on drug use and personality as well as the Symptom Checklist-90 (SCL-90).

MDMA users reported significantly greater usage of LSD and benzodiazepines than control subjects. They had higher scores on the “disturbed sleep” scale than controls, also when compared only to the subgroup of entirely drug-free controls. There were no differences between light and heavy users. However, the mean score of sleep disturbances (0.7) did not indicate a clinical condition (cut-off 1.0). Furthermore, ecstasy users had elevated scores on the subscales obsession-compulsion, phobic anxiety and psychoticism.

This study has similar weaknesses as the preceding one, most notably the failure to account for recent drug consumption and the differences in use of other agents.

Verheyden et al. (2003) obtained information on the subjective effects of MDMA in 430 regular ecstasy users from London and Manchester. Mean age was 24 and 45% were female. Individuals had used ecstasy for a mean of 5.2 years. When they first started to use ecstasy, less than 1% never used other drugs in combination with ecstasy. 59% reported they always consumed ecstasy conjointly with other substances. The subjects completed a questionnaire of 21 short-term MDMA effects and 16 long-term effects, to be marked as “yes” or “no”. Also, potential reasons for quitting ecstasy use in the future were investigated.

9% of participants complained of trouble sleeping within the first 24 hours after ecstasy consumption. The acute effects experienced most often were “euphoric rush” (92%) and “feeling warm towards others” (64%). Between 24 and 48 hours of use, 34% reported trouble sleeping and 40% having difficulty getting up on the subsequent day. Together with loss of appetite, these sleep effects constituted the most frequent effects between 24 and 48 hours of ecstasy use. During the course of the following week, 83% had ever had low mood and 80% difficulty concentrating.

With respect to the perceived long-term consequences, 21% mentioned chronic trouble sleeping which they attributed to ecstasy use. 18% reported feeling worn out. Complaints of developing tolerance to ecstasy effects (59%), impaired concentration (38%) and depression (37%) were referred to even more frequently. Fears for long-term mental health were cited as the most important reason (67%) why subjects might stop using ecstasy in the future.

The symptom severity was not assessed by the questionnaires. The identification of acute, but also of chronic effects relies exclusively on the subjective attribution of symptoms to ecstasy use. However, these symptoms are also influenced by concomitantly abused drugs and by a large variety of psychosocial variables.

A single case of persisting severe sleeping problems even after seven years of abstinence from ecstasy is reported by Soar et al. (2004). The case was considered noteworthy because it appears to demonstrate very little potential of recovery from the long-term effects of heavy ecstasy usage. The
patient was a young Caucasian male (age 26), who had a total lifetime consumption of 750 ecstasy tablets, in addition to a large variety of other recreational drugs. There was a family history of depression and anxiety.

The patient’s history and thorough neuropsychiatric examination revealed extremely high pathology that developed during his years of ecstasy abuse and which was typical of findings in heavy MDMA users (e.g. deficits in verbal recall and executive functioning). His symptoms did not alleviate over the seven years which he abstained from ecstasy. Hence, although the causality cannot be determined, his symptoms, including the severe sleeping problems, were attributed to his ecstasy use both by the patient and by the investigators.

The limitations of this article are obvious. Aside from being only a single case, the patient’s psychopathological problems may also have originated from the use of other substances, or their occurrence may be entirely independent of drug use.

3.2.2.5. Overview over sleep effects of ecstasy

In rats, acute administration of MDMA increases SOL and decreases light and deep SWS (see Table 22). REM sleep is reduced to an even greater extent.

Acute administration of MDE in humans increases wakefulness, as evidenced by an increase in WASO and by a reduction in TST and SE. MDE suppresses REM sleep. In heavy ecstasy users, there appear to be permanent alterations in polysomnographically monitored sleep. However, the pattern of alterations differed between studies.

Ecstasy users often report a more disturbed, restless sleep for at least 48 hours following drug ingestion. Heavy ecstasy use may be associated with chronic, persistent sleep disturbances.

<table>
<thead>
<tr>
<th>Entactogens</th>
<th>Acute administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOL</td>
<td>▲</td>
</tr>
<tr>
<td>WASO</td>
<td>↑</td>
</tr>
<tr>
<td>TST</td>
<td>↓</td>
</tr>
<tr>
<td>SE</td>
<td>↓</td>
</tr>
<tr>
<td>Stage 2 sleep</td>
<td>↓</td>
</tr>
<tr>
<td>Total SWS</td>
<td>-</td>
</tr>
<tr>
<td>REM sleep %</td>
<td>↓↓</td>
</tr>
<tr>
<td>REM sleep latency</td>
<td>↑↑</td>
</tr>
<tr>
<td>REM density</td>
<td>↓</td>
</tr>
</tbody>
</table>

Table 22: Overview over the sleep effects of entactogens; ▲▼ arrows indicate findings only from preclinical studies; ↑↓ arrows for studies in humans; - indicates no change
3.2.3. D-Lysergic acid diethylamide (LSD)

3.2.3.1. Study characteristics
Out of the twelve articles eligible for analysis, there were nine animal experiments, one cross-sectional study and two clinical trials (Table 23). Out of the studies in humans, all three employed PSG. No study on the subjective effects of LSD upon sleep was identified (Table 24). All of the papers date back to the 1960's and 1970's. No research on this agent's sleep effects has been carried out in recent years. The scientists' apparent loss of interest in this matter is a surprising and remarkable fact.

<table>
<thead>
<tr>
<th></th>
<th>Preclinical study</th>
<th>Case report</th>
<th>Cross-sectional study</th>
<th>Cohort study</th>
<th>Case-control study</th>
<th>Clinical study</th>
<th>Sum</th>
</tr>
</thead>
<tbody>
<tr>
<td>LSD</td>
<td>9</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>12</td>
</tr>
</tbody>
</table>

Table 23: Classification of the analyzed studies on LSD and sleep

<table>
<thead>
<tr>
<th></th>
<th>PSG study</th>
<th>Subjective effects</th>
<th>Sum</th>
</tr>
</thead>
<tbody>
<tr>
<td>LSD</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 24: Classification of studies in humans investigating the effect of LSD upon sleep

3.2.3.2. Preclinical studies
There are nine animal experiments which investigated the acute effects of LSD upon sleep (see Table 25). Seven of these are in full agreement. However, Hartmann (1967) presents findings which contradict the other studies. Bilkova et al. (1971) did not find any significant effects of LSD on behavioral state, possibly due to a methodological circumstance.
Table 25: Studies investigating the sleep effects of acute LSD administration in animals

<table>
<thead>
<tr>
<th>Publication</th>
<th>Purpose of study</th>
<th>Subjects</th>
<th>Administration protocol and recordings</th>
<th>Results</th>
</tr>
</thead>
</table>
| Hobson, 1964        | effects of LSD on sleep in cats   | 8 adult cats                                                             | intraperitoneal injection of placebo, 2 or 20 µg/kg LSD in 2 cats and 2 µg/kg LSD in 6 cats, recording over 2-4 h | • decrease in REM sleep  
  • increase in wakefulness (NS)                                        |
| Khazan and Sawyer, 1964 | to investigate the nature of REM sleep | 15 adult female New Zealand white rabbits                               | aside from other psychoactive agents, i.v. administration of 50 µg/kg LSD, EEG recordings and observations of behavior | • suppression of REM sleep for 3-5 h  
  • increase in wakefulness                                              |
| Hartmann, 1967      | effects of LSD on sleep in rats   | 2 male Charles River rats (in LSD arm), age 6 months                     | intraperitoneal injection of placebo or 2.5, 3.75, 5 or 10 µg LSD, 5 h recordings starting 30 min after injection | • increase in total REM sleep and REM%  
  • TST not affected                                                      |
| Depoortere and Loew, 1971 | effects of LSD on sleep in rats | unknown number of adult male Wistar rats                                | intraperitoneal administration of 1 mg/kg LSD, 6 h recordings following injection                      | • during first 4 h: increase in wakefulness  
  • reduction in SWS  
  • decrease in REM sleep                                                   |
| Bilkova et al., 1971 | effect of LSD on REM sleep in rats | 10 female rats, age 2-3 months                                           | subcutaneous infusion of 125 µg/kg LSD over 80 min, then, saline for 80 min (8 rats) or 125 µg/kg LSD over 60 min (2 rats), EEG for <4 h after end of initial LSD infusion | • no changes in TST, duration of NREM or REM sleep  
  • increase in frequency of hippocampal theta activity during REM sleep |
| Stern et al., 1972  | effects of LSD on sleep and PGO spikes during REM sleep in cats | 11 female cats (in LSD arm)                                             | intraperitoneal injection of 10-20 or 40 µg/kg LSD, recording over 10 h and for 6 h of the following day | • 10-20 µg/kg: decrease of REM sleep  
  • 40 µg/kg: increase in wakefulness, decrease in NREM sleep, almost total suppression of REM sleep |
| Brooks, 1975        | effects of LSD on PGO spikes in cats | 8 adult cats                                                             | numerous LSD dosages between 2-5 and 800 µg/kg intraperitoneal, each dose in at least 5 cats          | • arousal during first 2 h (doses of at least 20 µg/kg)  
  • increase in REM latency                                               |
| Kay and Martin, 1978 | effects of LSD and of tryptamine on sleep in cats | 4 male cats (in LSD arm)                                                | i.v. infusion of 3.75, 7.5, 15 µg/kg LSD over 5 min, recording over 225 min                         | • 0-75 min after infusion onset: decrease in spindle sleep  
  • 0-150 min: increase in wakefulness  
  • 0-225 min: decrease in REM sleep                                       |
| Polc et al., 1979   | effects of psychoactive drugs on sleep in cats | unknown number of adult male cats (in LSD arm)                          | intraperitoneal infusion of 2 µg/kg LSD, immediate recordings over 6 h and on subsequent days         | • marked decrease in NREM sleep  
  • complete suppression of REM sleep                                      |

Hobson (1964) injected a single dose of 2 or 20 µg/kg LSD or saline placebo intraperitoneally in two adult cats in a cross-over design with a three-day interval between LSD applications. Drug administration was performed after submitting the cats to 15 hours of exercise. Sleep EEG recordings were obtained for 2 to 4 hours. In a subsequent experiment, six additional cats received 2 µg/kg LSD or saline placebo with an interval of at least one week between trials.

There was a statistically significant decrease in total REM sleeping time, if the means from the higher dose and placebo were compared. REM sleep latency was increased. The higher dose was associated with a significant decrease in mean duration of REM periods. Wakefulness was increased, however not significantly. In the second experiment, REM sleep percentage and REM sleep mean duration after LSD injection was decreased compared to placebo.

The study does not contain any obvious biases.
In order to shed more light on the nature of REM sleep, Khazan and Sawyer (1964) carried out experiments in 15 adult female New Zealand white rabbits. They observed EEG tracings and behavior after administration of a number of psychoactive agents including LSD and after electrical stimulation of the midbrain reticular formation. 50 µg/kg of LSD were administered i.v. in a non-specified number of rabbits.

The authors report that REM sleep was inhibited for 3 to 5 hours after administration. Also, cortical evoked responses to stimulation of the reticular formation were enhanced after LSD administration, indicating increased alertness.

The article provides little information about details of the study protocol and results. Another apparent weakness is the fact that the study lacks a control group and statistical analyses.

Hartmann (1967) conducted experiments in rats to substantiate the serotonin theory of dreaming. Two six-month-old, male Charles River rats, weighing about 500 g, were injected placebo or 2.5, 3.75, 5, and 10 µg/kg LSD intraperitoneally at 9:30 A.M. There were intervals of 3 to 4 days between administrations. EEG and EMG recordings were obtained for five hours, starting at 10 A.M. In a separate experiment, rats were administered a tryptophan-free diet or an excess of tryptophan, the amino acid from which serotonin is synthesized.

Total REM sleep and REM sleep percentage were significantly increased after LSD injection, and the sleep cycle length was reduced. TST was not affected by administration of LSD. Sleep cycle length was increased in rats receiving tryptophan-free diet and decreased in animals offered a tryptophan excess. Both diets appeared to disturb sleep, yet the decrements in TST were non-significant.

Apparently, the study was well conducted. One limitation is the small sample size in the LSD experiment (n=2). The LSD doses administered in this study were lower than in most comparable studies. Maybe this explains the differences in the observed results.

In a short communication, Depoortere and Loew (1971) report about experiments with an unknown number of adult male Wistar rats. 1 mg/kg of LSD was administered intraperitoneally, followed by six hours of recordings.

Injection of the drug produced statistically significant alterations of the sleep-wake cycle during the first four hours of recordings. There was an increase in wakefulness, a reduction in SWS and, more pronounced, in REM sleep. The drug effects were most prominent during the first hour and diminished gradually. In hours five and six, no significant alterations of the sleep profile were detected.

The paper does not furnish any information about the recording technique, sleep state definition or the statistical methods that were employed, which makes a critical analysis impossible.

In the study by Bilkova et al. (1971), ten female rats (aged 2 to 3 months) were injected saline placebo subcutaneously for two hours after onset of continuous SWS. This was followed by the subcutaneous administration of 125 µg/kg LSD over 60 minutes. In two animals, this dose was repeated immediately afterwards. The other rats received a subsequent saline infusion. It cannot be made out exactly for how much time EEG recordings were obtained after the end of the infusion, but it was not more than four hours after the initial LSD administration.
There were no significant changes in TST, total duration of SWS or REM sleep or in the respective percentages. The only significant finding was an increase in the frequency of hippocampal theta activity during REM sleep.

In contrast to the remaining studies, sleep stages were not affected by LSD application in this experiment. This deviating finding may be a result of the different route of administration. The resorption of the substance was delayed due to the subcutaneous injection. Hence, the agent may only have started to act at the end of the recordings. Differential data upon the sleep stages per hour are not given, only the totals for the entire observation period were considered in the analyses.

In the study by Stern et al. (1972), eleven female cats were administered 10 to 20 µg/kg (n=4) or 40 µg/kg (n=7) of LSD intraperitoneally after at least 3 baseline recording days. EEG recordings were obtained for the following ten hours and for another six hours on the subsequent day. There were also experiments with brom-LSD, a substance that acts as a potent antagonist on peripheral serotonin receptors. Brom-LSD does not have any hallucinogenic effects.

When given in the lower dosage, LSD produced only a reduction in REM sleep. After the 40 µg/kg dose, wakefulness was increased, SWS decreased and REM sleep was almost suppressed entirely (from 13% at baseline to 2%). On the following day, sleep patterns returned to normal values. Furthermore, the percentage of ponto-geniculo-occipital (PGO) spikes occurring during REM sleep declined substantially after the higher dose, and this effect persisted on the subsequent day. Sleep patterns remained unchanged after brom-LSD.

No biases were found in the critical analysis of the article.

The effects of LSD upon PGO spikes in cats were also investigated by Brooks (1975). LSD was administered intraperitoneally in eight different dose levels between 2 and 800 µg/kg. Each dose was tried in at least 5 cats. EEG was recorded continuously for 10 to 48 hours. No statistical analyses were performed.

During the first two hours, doses over 20 µg/kg increased wakefulness in a dose-dependent manner. There was a dose-dependent increase in REM sleep latency until long after the acute effects had subsided. For instance, REM sleep occurred only eight hours after administration of the 200 µg/kg dose. PGO spikes with the characteristics of those in REM sleep did not occur during waking. Since the study is merely descriptive, the validity of the observations is not clear.

Kay and Martin (1978) compared the effects of LSD upon sleep waking patterns in cats with those of tryptamine. The study was designed as a placebo-controlled, cross-over trial. Four male cats were infused either 3.75, 7.5 or 15 µg/kg of LSD i.v. over 5 minutes. Saline control infusions were administered over a period of 150 minutes. A hippocampal EEG, two electrocorticograms (ECoGs), EMG and EOG recordings were obtained over 225 minutes. At least seven days elapsed after each LSD experiment.

During the first 75 minutes after infusion onset, there was a significant increase in active wakefulness, and, for the higher doses, a decrease in spindle sleep and REM sleep. During the following 75 minutes, there continued to be an increase in wakefulness. REM sleep was suppressed completely for
the higher doses. EEG δ spectral power was increased significantly and dose-dependently, whereas α, σ and β spectral powers were decreased. The decrease in REM sleep was still significant during the last 75 minutes of recordings.

The study was well-conducted.

Polec et al. (1979) examined the effects of a variety of psychoactive drugs upon the sleep of cats. 108 adult male cats were infused control saline intraperitoneally at 9 A.M. for three consecutive days. This was followed by the administration of one of the active substances. These were several antidepressants, but also antipsychotics, 5-hydroxytryptophan, cyproheptadine and LSD. The LSD dose employed was 2 µg/kg. EEG and EMG recordings were obtained for six hours following infusion, and also on the four subsequent days. There were intervals of at least two weeks between drug administrations.

REM sleep was suppressed completely after LSD administration. NREM sleep was reduced to only 25% of baseline values. Both findings were statistically significant. Although in exchange wakefulness was increased considerably, no apparent psychomotor excitation was noted.

The study does not contain any obvious biases.

### 3.2.3.3. PSG studies of LSD ingestion

There are two studies in humans that investigated the acute effects of LSD upon REM sleep (Muzio et al., 1966; Green, 1969) and one study on the longer-term sleep effects of LSD (Meier-Koll, 1974; see Table 26).

<table>
<thead>
<tr>
<th>Publication</th>
<th>Purpose of study</th>
<th>Subjects</th>
<th>Study design, administration protocol and outcome measures</th>
<th>Results</th>
</tr>
</thead>
</table>
| Muzio et al., 1966 | effects of LSD upon REM sleep | 6 female and 6 male volunteers ages 19-30 | • SB, non-randomized, controlled study  
• oral administration of placebo or 0.1-0.7 µg/kg LSD just prior to sleep or 1 h after falling asleep  
• 7 d between administrations  
• mean of 3 drug nights per subject  
• EMG only in 4 subjects  
• no statistical analysis | • increase in duration of either first or second REM period in 21 of 36 instances  
• decrease in duration of subsequent REM periods  
• REM sleep latency and total REM sleep unchanged  
• 12 awakenings in the 36 instances |
| Green, 1969     | effects of LSD upon REM sleep | 1 male chronic alcoholic age 38 | • open, non-randomized study  
• 2 baseline nights, a week later administration of 300 µg LSD at noon, two follow-up nights  
• apparently, only EEG recordings and bedside observer  
• no statistical analysis | • increase in total REM sleep  
• increase in REM latency  
• increase in body movements  
• total REM sleep increased even more on follow-up night |
| Meier-Koll, 1974 | sleep patterns of teenagers with chronic drug abuse | 5 male teenagers with use of LSD, also cannabis ages 16-21 | • cross-sectional study  
• PSG recordings of one night  
• no statistical analysis | • increase in REM sleep in subjects whose last trip only 1-2 wk ago  
• reduced REM latency  
• reduction in SWS |

Table 26: Studies examining the acute and chronic effects of LSD in humans
The two studies on acute sleep effects of LSD in humans started out from the hypothesis that, in view of the similarities between dreams and the hallucinatory state produced by LSD, this agent may increase dreaming time and, hence, REM sleep.

12 young volunteers (19 to 30 years of age; six of them female) participated in the single-blind study by Muzio et al. (1966). Subjects were aware that they would receive LSD on some of the nights. LSD or placebo was administered orally just prior to sleep or one hour after falling asleep. The initial total dose was 25 to 30 µg, but in view of the arousing effects of this dose, the starting dose was lowered to 7 to 22 µg. Then, depending on the subject’s response, his dose was modified in the following trials. The study was carried out before the development of sleep EEG scoring criteria (Rechtschaffen and Kales, 1968) and it performed EMG recordings only in four subjects. On the whole, there were 69 pre-drug nights, 36 LSD nights and 13 follow-up nights. In 21 out of the 36 LSD nights, there was an increase in the duration of either the first or the second REM period, associated with a decline of the subsequent REM sleep periods so that total REM sleeping time was not altered. REM sleep latency was not affected either. There were twelve awakenings in the 36 instances. A few subjects reported visual hallucinations and one described synesthesias. The follow-up nights were comparable to the pre-drug nights.

A few serious biases were found in the critical analysis of this study. EMG recordings are indispensable for the definition of REM sleep. Without them, the eye movements and EEG desynchronization of waking can be mistaken for REM sleep. The investigators fail to state in which subjects EMG recordings were registered. A further methodological problem is the circumstance that the investigators changed the study protocol ex post and lowered the initial LSD dose in order to minimize the arousing effects of the drug. Also, they arbitrarily modified each participant’s LSD dose depending on their reaction to the previous one, and they arbitrarily determined for how many drug nights each subject was tested. The study is merely descriptive and does not substantiate its findings with statistical analyses.

Green (1969) studied LSD effects upon the REM sleep of a chronic alcoholic patient, 38 years of age. Since he was in an inpatient facility for an alcoholic treatment program, it is assumed that he was abstinent for an undetermined period of time at the moment of the trial. After two consecutive baseline nights, there was a one-week interval before the LSD experiment. The patient was administered 300 µg LSD orally already at noon of the experimental day. There was no blinding, and the individual reportedly apprehended experiencing the drug’s effects. EEG recordings were performed during that and the two following nights. Since the actual study had been carried out in 1965, it did not follow the sleep EEG scoring criteria by Rechtschaffen and Kales (1968). EMG was not recorded, and presumably, the eye movements were protocoted by a bedside observer. There was an increase in total REM sleep and REM sleep percentage on the experimental night. At the same time, REM sleep latency was increased. Body movements were augmented. An additional increase in total REM sleep was observed on the first follow-up night. After that night, total REM sleep returned to baseline.
The study appears to be flawed by severe weaknesses. First of all, sleep stages were defined in the absence of EMG recordings. However, as mentioned above, these are indispensable for an unambiguous identification of REM sleep. Moreover, the investigator fails to take into consideration that the patient’s alcoholism or withdrawal from alcohol per se may amount to important alterations of REM sleep. The two baseline nights had REM sleep percentages of 18% and 22%, although measures would be expected to be high in a young alcoholic during withdrawal. An REM sleep percentage of 26.5% as during the experimental night usually would not be considered elevated in a young abstinent alcoholic. As mentioned before, there was no blinding, which had a relevant impact upon the subject’s expectations. The administration of LSD was already about 12 hours before bedtime. The increase in REM sleep latency and the fact that REM sleep was only increased in the second half of the night are not consistent with the investigator’s hypothesis of an REM-sleep enhancing effect of LSD. This is true also for the fact that total REM sleep was increased even more during the first follow-up night. Moreover, the one-week interval between baseline recordings and experimental day might have been too long in terms of potential changes in the patient’s general state during this period. No statistical analyses were performed.

The longer-term effects of LSD use upon sleep were assessed only by a single study (Meier-Koll, 1974). The participants of this study were ten male adolescent drug users (ages 16 to 21). Five of them were intravenous opiate abusers. The other five had a pattern of LSD use of “once in a few weeks”, and smoked marijuana intermittently. The last episode of their LSD use had been one to two weeks before the trial in three subjects and more than that in the other two. No statement is made about concomitant psychiatric disorders and medications. Subjects were submitted to a single night of PSG recordings, no drug was administered. The tracings were compared to an age-matched group of healthy controls with no prior history of substance use. Those three subjects with LSD exposure within the past 1 or 2 weeks had a substantial increase in REM sleep and a decrease in REM latency compared to control subjects. Moreover, SWS was reduced in exchange for a relative increase in stage 2 sleep. The investigator states that in the other two LSD users the alterations were less prominent.

These findings need to be interpreted cautiously. It is not clear whether there was an adaptation night before recordings, and only a single night was examined. Apparently, no statistical analyses were performed. The extent of the marijuana use and the interval since last use were not specified. The question of a potential contribution of the reported cannabis use deserves attention in view of the fact that the individuals’ sleep patterns would also be consistent with those of chronic marijuana users (Karacan et al., 1976) and cannabis withdrawal (Feinberg et al., 1976). Furthermore, the alterations could only be interpreted as long-term effects of LSD if psychiatric comorbidity was ruled out and if PSG recordings before the onset of LSD use were available and showed lack of preexisting abnormalities. Since the sleep effects appeared to decline with increasing time since last LSD use, they would not constitute lasting neurophysiologic alterations as proclaimed by the investigator. The remaining studies did not detect any residual sleep effects of LSD after more than two nights of ingestion (Muzio et al., 1966; Green, 1969; Stern et al., 1972).
3.2.3.4. Overview over effects of LSD upon sleep

Animal experiments suggest that administration of LSD increases wakefulness (see Table 27). REM sleep is reduced to a greater extent than NREM sleep. One study indicated that in rats, low doses of LSD may increase REM sleep.

The two studies in humans that assessed the acute effects of LSD upon sleep are suggestive of an increase in REM sleep. Yet, these trials contain some serious biases which warrant cautious interpretation of the findings. The existing evidence on the longer-term sleep effects of LSD needs to be considered as inconclusive.

<table>
<thead>
<tr>
<th>LSD</th>
<th>Acute administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOL</td>
<td>✓</td>
</tr>
<tr>
<td>WASO</td>
<td>✓</td>
</tr>
<tr>
<td>TST</td>
<td>✓</td>
</tr>
<tr>
<td>REM sleep %</td>
<td>✓</td>
</tr>
<tr>
<td>REM sleep latency</td>
<td>✓</td>
</tr>
</tbody>
</table>

Table 27: Overview over effects of LSD upon sleep; ✓▼ arrows indicate findings only from preclinical studies; ↑↓ arrows for studies in humans

3.2.4. Cannabis

3.2.4.1. Study characteristics

41 studies were eligible for analysis. Out of these, there were nine preclinical studies, one case report, four cross-sectional studies, three cohort studies and 24 clinical trials (see Table 28). Out of the studies in humans, 13 assessed sleep by means of PSG, one with a bedside observer, one with wrist actigraphy, 15 with subjective ratings and two examined effects of prenatal exposure to cannabis (see Table 29). There has been more research on the sleep effects of cannabis than for any of the other substances considered in this dissertation.

<table>
<thead>
<tr>
<th></th>
<th>Animal experiments</th>
<th>Case report</th>
<th>Cross-sectional study</th>
<th>Cohort study</th>
<th>Case-control study</th>
<th>Clinical study</th>
<th>Sum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannabis</td>
<td>9</td>
<td>1</td>
<td>4</td>
<td>3</td>
<td>0</td>
<td>24</td>
<td>41</td>
</tr>
</tbody>
</table>

Table 28: Classification of the analyzed studies on cannabis and sleep
Table 29: Numbers of sleep studies of cannabis in humans

<table>
<thead>
<tr>
<th>Cannabis</th>
<th>PSG studies</th>
<th>Bedside observer</th>
<th>Actigraphy</th>
<th>Subjective ratings</th>
<th>Prenatal exposure</th>
<th>Sum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>13</td>
<td>1</td>
<td>1</td>
<td>15</td>
<td>2</td>
<td>32</td>
</tr>
</tbody>
</table>

3.2.4.2. Preclinical studies

Sleep effects of acute cannabis administration in animals

There are five preclinical studies that investigated the sleep effects of acute administration of marijuana extract or tetrahydrocannabinols (see Table 30), and two studies of chronic administration. In two further experiments, the sleep effects of cannabidiol (CBD) are studied.

<table>
<thead>
<tr>
<th>Publication</th>
<th>Purpose of study</th>
<th>Subjects</th>
<th>Administration protocol and recordings</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fujimori and Himwich, 1973</td>
<td>sleep effects of Δ-9-THC in rabbits</td>
<td>6 adult male New Zealand albino rabbits</td>
<td>i.v. injection of vehicle, 0.5 mg/kg and 1.0 mg/kg Δ-9-THC; 5-h recordings immediately after injection and on the two following days</td>
<td>initial increase in wakefulness; decrease at hour 4, initial decrease of SWS, increase at hour 4, decrease in REM sleep at hours 1-3</td>
</tr>
<tr>
<td>Wallach and Gershon, 1973</td>
<td>effects of Δ-8-THC on the cat EEG</td>
<td>presumably n=12 adult cats in sleep experiments</td>
<td>administration of 10 mg/kg intraperitoneally, 1 mg/kg i.v., 4 mg/kg i.v. of Δ-8-THC; recording of reticular formation multiple unit activity</td>
<td>drowsiness, REM sleep completely suppressed for 6-9 hours, total REM sleep not altered on day 1, but increased on days 2 and 3 (1 mg/kg i.v.)</td>
</tr>
<tr>
<td>Moreton and Davis, 1973</td>
<td>effects of Δ-9-THC and MED upon sleep in rats</td>
<td>paradoxical sleep deprived and non-deprived adult male Wistar rats n=3 for all subgroups of acute experiments n=2 for all subgroups of chronic experiment preliminary observations in cats</td>
<td>acute experiments: intraperitoneal injection of 10 mg/kg Δ-9-THC, recordings for 24 h chronic experiment: daily intraperitoneal injection of 10 mg/kg Δ-9-THC or vehicle recordings for 15 h, 3 d pre-drug, 20 d treatment, 12 d post-drug, 1 d retest deprivation of paradoxical sleep only during the 9 h non-recording portion of day experiments in cats: single-dose of 10 mg/kg Δ-9-THC</td>
<td>acute experiments: increase in wakefulness, trend for reduction in SWS, reduction in REM sleep paradoxical sleep deprived rats: blockage of REM rebound confirmatory experiment: non-deprived rats: decrease in REM sleep and SWS, increase in wakefulness paradoxical sleep deprived rats: blockage of REM rebound, increase in SWS chronic experiment: decrease in REM sleep on days 1 and 2 drug administration on retest day with no reduction in REM sleep in cats: similar observations, REM rebound on first post-drug day in non-deprived cats</td>
</tr>
<tr>
<td>Monti and Carlini, 1975</td>
<td>effects of marijuana on sleep in different conditions</td>
<td>17 male Wistar rats 250-300 g</td>
<td>intraperitoneal administration of placebo or 10 mg/kg of a marijuana extract in both cases, with or without 4 d of deprivation of paradoxical sleep recordings for 8 h, beginning 20 min after injection</td>
<td>isolated rats: increase in REM latency isolated, paradoxical sleep deprived rats: no difference between marijuana and placebo paired rats: decrease in SWS and REM sleep paired, paradoxical sleep deprived rats: continuous wakefulness</td>
</tr>
<tr>
<td>Buonamici et al., 1982</td>
<td>acute effects of Δ-9-THC on EEG in rat</td>
<td>15 adult female Sprague-Dawley rats</td>
<td>intraperitoneal administration of two doses of 5 or 10 mg/kg Δ-9-THC at 9 A.M. to 2 groups of 5 rats baseline placebo recordings continuous recordings of EEG and EMG, power spectral analysis</td>
<td>during wakefulness: desynchronized EEG spectral power reduced during first hour, gradually returning to control values SWS and REM sleep emerging early SWS: increase in slow-frequency power REM sleep: overriding high-voltage bursts</td>
</tr>
</tbody>
</table>

Table 30: Studies investigating the sleep effects of acute administration of cannabis, either as Δ-9-THC, Δ-8-THC or marijuana extract, in animals
Fujimori and Himwich (1973) examined the sleep effects of delta-9-tetrahydrocannabinol (Δ-9-THC) in six adult male New Zealand albino rabbits. After control values after administration of vehicle had been obtained, the rabbits were injected 0.5 mg/kg of Δ-9-THC i.v. and monitored polysomnographically for five hours on that and on the following two days. This protocol was repeated after two weeks with a dose of 1.0 mg/kg Δ-9-THC.

The lower dose was associated with an increase in wakefulness during the first hour after injection, and a reduction during the fourth hour. SWS changed in the opposite direction with an initial non-significant decrease and a significant increase at four hours. REM sleep was suppressed during the first three hours through a reduction in the number of REM sleep episodes. The effects of the higher dose upon behavioral state were similar, however even more pronounced.

On the second day, wakefulness was increased and REM sleep still decreased significantly (the latter only for the higher dose). Values reached baseline levels by the third day.

Continuous recordings would have been more appropriate in this study. Without them, the alterations in behavioral state on the second day are difficult to interpret.

Wallach and Gershon (1973) experimented with Δ-8-THC, since it was suggested that Δ-9-THC may be converted to Δ-8-THC upon burning (Lerner and Zeffert, 1968). Today, this process has not proven to be of greater relevance. Although the exact number is not given, presumably twelve cats were included in the sleep studies. Δ-8-THC was administered intraperitoneally at a dose of 10 mg/kg, whereas intravenous doses were 1 mg/kg or 4 mg/kg of Δ-8-THC. Sleep states were defined using the recordings of the reticular formation multiple unit activity.

Ataxia and sedation characterized gross behavior after drug administration. SWS was difficult to estimate owing to extended periods of drowsiness. REM sleep was completely suppressed for six hours after 1 mg/kg Δ-8-THC i.v. and for nine hours after 4 mg/kg. The intraperitoneal administration of 10 mg/kg Δ-8-THC was associated with a total REM sleep suppression for seven hours. Total REM sleep was not altered on the first day, so apparently there was an REM rebound after the first six to nine hours. Total REM sleep was increased on days two and three for the 1 mg/kg i.v. dose level. The average duration of each REM sleep episode was increased significantly for the 1 mg/kg i.v. dose on the experimental day, which occurred during the REM rebound after the sixth hour.

Sleep state definition was unconventional in this study. It did not allow for differentiation of SWS. It is not clear whether this method registered REM sleep measures reliably enough.

Moreton and Davis (1973) conducted extensive preclinical studies on the sleep effects of Δ-9-THC, Δ-8-THC and marijuana extract distillate (MED). In addition to experiments with adult male Wistar rats weighing 200 to 300 g, the article reports about preliminary observations in cats. Rats were either paradoxical sleep deprived for 72 hours or non-deprived. Paradoxical sleep deprivation was performed in order to gain additional insight on the effects of cannabinoids upon REM sleep. It was hypothesized that cannabinoids might block the REM rebound usually observed after REM sleep deprivation. The acute experiments with either 5 mg/kg or 10 mg/kg of each of the three substances (Δ-9-THC, Δ-8-THC, MED) were performed in three paradoxical sleep deprived and three non-deprived rats. Drugs were administered intraperitoneally during the light phase. EEG and EMG tracings were registered for
three hours starting one hour after injection and on five post-drug days. EOG was recorded in two rats only. The initial lack of 24-hour recordings prompted the investigators to perform confirmatory experiments during which EEG was registered continuously. They were conducted with 10mg/kg of Δ-9-THC in paradoxical sleep deprived and non-deprived rats. In the chronic experiments, there were two rats for each subgroup. There was a daily intraperitoneal injection of either 10mg/kg Δ-9-THC or vehicle for twenty days. Rats were deprived of paradoxical sleep only during the nine-hour non-recording portion of the day. Paradoxical sleep was restricted during three pre-drug days, during the twenty days of treatment and on twelve consecutive abstinence days. After this withdrawal period, drug administration was repeated on one day. In a preliminary experiment, a single dose of 10mg/kg Δ-9-THC was administered to paradoxical sleep deprived and non-deprived cats.

Acute drug administration in rats induced ataxia and an initial agitation. In non-deprived rats, SOL was increased significantly only for 10mg/kg MED and REM sleep was reduced for all conditions except for 5mg/kg MED. There was an absence of phasic events of REM sleep such as eye movements. There was a trend for a reduction in SWS. Paradoxical sleep deprived rats showed the expected rebound in paradoxical sleep after placebo, but this rebound was blocked after all non-placebo treatments except for 5mg/kg MED.

The confirmatory experiments demonstrated the same increase in wakefulness and reduction in REM sleep. REM density appeared to be reduced, but was not quantified. Furthermore, the decrease in SWS achieved statistical significance. These effects only occurred during the light phase. Measures returned to baseline levels on the first recovery day. Paradoxical sleep deprived rats did not show an REM rebound after administration of Δ-9-THC. Additionally, SWS was increased.

During the chronic experiments, REM sleep was only decreased during the first two days compared to control values. Rats then quickly developed tolerance to the REM sleep effect. Upon withdrawal, there was no REM rebound, and re-administration of Δ-9-THC after thirteen days did not produce a significant decrease in REM sleep.

The results of the preliminary observations in cats were similar, with the exception that an REM rebound was detected on the first post-drug day.

The study was conducted well. However, the great number of different study arms resulted in small sample sizes (n=2 to 3) for each condition and makes the interpretation difficult.

Monti and Carlini (1975) compared isolated and paired, paradoxical sleep deprived and non-deprived rats with respect to behavior and sleep after administration of marijuana. 17 male Wistar rats were injected placebo or 10 mg/kg of marijuana extract intraperitoneally. The marijuana extract contained 6.9 mg of Δ-9-THC. Rats were also run on this schedule after four days of REM deprivation. In addition to experiments in individual cages, two similarly exposed rats were introduced together in a paired cage for each condition except for the non-deprived placebo rats. This procedure was intended to shed light upon whether marijuana effects depended on the animals’ environment. Seven rats were caged individually, and apparently ten rats were used for the paired experiments. EEG recordings were obtained starting 20 minutes after injection for a total duration of eight hours. There was an interval of at least one week between experiments.
Marijuana effects differed considerably depending on the rat’s environment. In isolation, non-deprived rats had a significantly increased REM sleep latency and a decrease in the number of REM sleep periods compared to placebo controls. Not achieving statistical significance, wakefulness was increased and total REM sleep reduced. No difference was reported between the marijuana-treated paradoxical sleep deprived rats and control paradoxical sleep deprived rats. On the other hand, when they were paired, non-deprived rats spent significantly less time in SWS and REM sleep than placebo controls. Paired, marijuana-treated, paradoxical sleep deprived rats even showed continuous wakefulness throughout the registration period.

The study does not contain any obvious biases.

The acute effects of Δ-9-THC upon the EEG of the rat were investigated by Buonamici et al. (1982). 10 adult female Sprague-Dawley rats were given two doses of either 5 or 10 mg/kg Δ-9-THC at 9 A.M., i.e. at the beginning of the light phase. Continuous EEG and EMG tracings were obtained for eight hours, and power spectral analysis was performed. Baseline recordings after administration of placebo served for control values. Apparently, there was another group of five rats who only received saline vehicle.

During wakefulness, rats appeared sedated. Their desynchronized EEG spectral power was reduced to about 50% of control values during the first hour, and gradually returned to normal values over the eight-hour registration period. SWS and REM sleep emerged early. SWS was characterized by an increase in high-voltage slow-frequency waves and spectral analysis revealed more power in the slow-frequency bands compared with control EEG. During REM sleep, overriding high-voltage bursts were observed.

Sleep measures were not quantified in this study.

Sleep effects of chronic cannabis administration and subsequent withdrawal

There are two preclinical studies that examined the sleep effects of chronic cannabis administration and withdrawal (Barratt and Adams, 1973; Adams and Barratt, 1975). The first was conducted with marijuana extract in cats, the second with Δ-9-THC in monkeys (see Table 31).

<table>
<thead>
<tr>
<th>Publication</th>
<th>Purpose of study</th>
<th>Subjects</th>
<th>Administration protocol and recordings</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barratt and Adams,</td>
<td>sleep effects of chronic marijuana and withdrawal in cats</td>
<td>6 adult</td>
<td>• 5 d baseline</td>
<td>• decrease in SWS starting on drug day 20 and persisting throughout</td>
</tr>
<tr>
<td>1973</td>
<td></td>
<td>male cats</td>
<td>• 180 d oral administration of MED, containing 2.7 mg/kg Δ-9-THC</td>
<td>withdrawal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 cats</td>
<td>• 40 d post-drug recovery</td>
<td>• increase in drowsy-light sleep from the 1st drug day through the 20th</td>
</tr>
<tr>
<td></td>
<td></td>
<td>with lower</td>
<td>• recordings for 15 min/h over 11 h on 10 d across treatment phase and on 6 d across withdrawal</td>
<td>post-drug day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>lower dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>cat</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adams and Barratt,</td>
<td>sleep effects of chronic Δ-9-THC and withdrawal in monkeys</td>
<td>8 adult</td>
<td>• 30 baseline days</td>
<td>• decrease in stage 2 sleep and increase in wakefulness during treatment phase</td>
</tr>
<tr>
<td>1975</td>
<td></td>
<td>male</td>
<td>• 60 d oral administration of 1.2 mg/kg Δ-9-THC (n=2 received placebo) at 4 P.M.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>squirrel</td>
<td>• 30 d post-drug recovery</td>
<td>• decrease in SWS and increase in stage 1 sleep throughout drug administration and withdrawal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>monkeys</td>
<td>• every 3 or 4 days, recordings for 20 min/h over 24 h, beginning at 5 P.M.</td>
<td></td>
</tr>
</tbody>
</table>

Table 31: Studies investigating the sleep patterns in animals after chronic administration of cannabis and during withdrawal.
In the study by Barratt and Adams (1973), six adult male cats were given, after five baseline days, a daily oral dose of MED containing 2.7 mg/kg Δ-9-THC for a period of 180 days. Two additional cats received a lower dose of MED containing 0.34 mg/kg Δ-9-THC for the same amount of time, and one cat was administered placebo. Drug administration was at 11 A.M. Sleep EEG tracings were obtained for 15 minutes per hour over 11 hours on 10 different days across the treatment phase. This was followed by 40 recovery days, with sleep EEG recordings on six different days.

There was a significant increase in the drowsy-light sleep between the first day of drug administration and day 20, and a decrease in SWS which started on drug day 20 and persisted for the rest of the treatment phase and throughout withdrawal. There were no consistent patterns of changes in REM sleep or wakefulness. Similar results were observed in the two cats receiving lower doses, and sleep remained unchanged across conditions in the placebo cat.

Recordings were not obtained every day. In fact, they were not even performed continuously on those days, but only for 15 minutes every hour over eleven hours. This might have confounded the study’s results.

A similar study was carried out by the same investigators in eight adult male squirrel monkeys (Adams and Barratt, 1975). In this study, Δ-9-THC was used instead of MED. After 30 baseline days, the primates received oral administrations of 1.2 mg/kg Δ-9-THC at 4 P.M. through 60 consecutive days. Two monkeys received placebo. Sleep EEG was registered for 20 minutes per hour for 24 hours starting at 5 P.M. on 18 instances over this period. Intervals between recordings were not longer than three days. During the 30-day recovery period, no drug was administered and EEG recordings were performed on nine different days.

SWS was decreased significantly throughout the treatment and recovery phases of the experiment, in exchange for an increase in stage 1 sleep, i.e. the drowsy state. During the treatment phase, stage 2 sleep was decreased significantly compared to baseline, and there was a significant increase in wakefulness compared to the control group. There were non-significant fluctuations of REM sleep measures: an initial decrease in REM sleep was followed by a subsequent increase on drug day 8. At the end of the 60 days, REM sleep was slightly reduced, which persisted during initial abstinence. At day 18 of withdrawal, REM sleep was increased.

Recordings were more frequent and lasted longer in this study, but they were not continuous either. Since the study was conducted in primates, the transfer of the findings to humans is more reliable.

Sleep effects of cannabidiol in animals

There are two preclinical studies which specifically examine the sleep effects of cannabidiol (CBD) upon sleep (Monti, 1977; Murillo-Rodríguez et al., 2006). Both were conducted in adult, male Wistar rats weighing 250 to 300 g. However, there were important differences in the CBD doses and route of administration (see Table 32).
Monti, 1977  
**Purpose of study**: effects of CBD upon sleep in rats  
**Subjects**: 8 male Wistar rats weighing 250-300 g  
**Administration protocol and recordings**: intraperitoneal administration of 20 or 40 mg/kg CBD (single dose) and of 40 mg/kg CBD for 15 d (lights-on period); recordings for 5 h, beginning 20 min after injection  
**Results**:  
- decrease in SOL  
- decrease in wakefulness and increase in SWS (only higher dose, especially first hour)  
- no changes in REM sleep  
- development of tolerance in chronic experiment

Murillo-Rodriguez et al., 2006  
**Purpose of study**: effects of CBD upon sleep in rats  
**Subjects**: 50 male Wistar rats weighing 250-300 g and another 24 rats for combination with anandamide  
**Administration protocol and recordings**: intracerebroventricular administration of placebo or 10 µg CBD, of 10 µg anandamide, or both (lights-on and lights-off period); recordings for 4 h after injection; immunohistochemistry for c-Fos and microdialysis for extracellular levels of neurotransmitters in nucleus accumbens  
**Results**:  
- lights-off period: no changes  
- lights-on period: increase in wakefulness, decrease in REM sleep  
- anandamide decreased wakefulness; yet, combination with CBD still increased wakefulness  
- c-Fos expression enhanced in medial preoptic nucleus and dorsal raphe nucleus  
- increase in extracellular dopamine, norepinephrine and serotonin in nucleus accumbens

<table>
<thead>
<tr>
<th>Publication</th>
<th>Purpose of study</th>
<th>Subjects</th>
<th>Administration protocol and recordings</th>
<th>Results</th>
</tr>
</thead>
</table>
| Monti, 1977                       | effects of CBD   | 8 male Wistar rats weighing 250-300 g | intraperitoneal administration of 20 or 40 mg/kg CBD (single dose) and of 40 mg/kg CBD for 15 d (lights-on period); recordings for 5 h, beginning 20 min after injection | decrease in SOL  
- decrease in wakefulness and increase in SWS (only higher dose, especially first hour)  
- no changes in REM sleep  
- development of tolerance in chronic experiment |
| Murillo-Rodriguez et al., 2006    | effects of CBD   | 50 male Wistar rats weighing 250-300 g and another 24 rats for combination with anandamide | intracerebroventricular administration of placebo or 10 µg CBD, of 10 µg anandamide, or both (lights-on and lights-off period); recordings for 4 h after injection; immunohistochemistry for c-Fos and microdialysis for extracellular levels of neurotransmitters in nucleus accumbens | lights-off period: no changes  
- lights-on period: increase in wakefulness, decrease in REM sleep  
- anandamide decreased wakefulness; yet, combination with CBD still increased wakefulness  
- c-Fos expression enhanced in medial preoptic nucleus and dorsal raphe nucleus  
- increase in extracellular dopamine, norepinephrine and serotonin in nucleus accumbens |

Table 32: Studies examining the effect of CBD upon behavioral state in animals

In the study by Monti (1977), eight Wistar rats were administered a single dose of either 20 or 40 mg/kg CBD intraperitoneally at the beginning of the lights-on period. Chronic experiments were also performed. In these, 40 mg/kg of CBD was administered for 15 consecutive days, also at the beginning of the light phase. EEG and EMG tracings were registered for five hours, starting 20 minutes after injection. There was an interval of at least one week which separated experiments in the same animal.

Acute administration of CBD decreased SOL for both dosages, and the 40 mg/kg dose additionally decreased wakefulness and increased SWS. This effect was most pronounced during the first hour. REM sleep was not affected. After repeated exposure to CBD, the acute sleep changes were not present any more, and sleep patterns did not differ from baseline levels.

CBD doses in this experiment were high (20 and 40 mg/kg). It would have been helpful to include also lower doses of CBD in the schedule which have more clinical relevance.

Murillo-Rodriguez et al. (2006) carried out intracerebroventricular administrations of placebo, 10 µg CBD (equivalent to about 30 µg/kg), 10 µg of the endocannabinoid anandamide and 10 µg of both to altogether 74 Wistar rats. The substances were injected at the beginning of the lights-on and the lights-off phase. EEG and EMG were registered for four hours after injection. Immunohistochemical staining for c-Fos was performed after the end of the experiments. Extracellular dopamine, noradrenaline, serotonin and 3,4-dihydroxy-L-phenylalanine (L-DOPA) and 5-hydroxy-indoleacetic acid (5-HIAA) levels in the nucleus accumbens were identified by microdialysis in 14 rats.

If administered at the beginning of the lights-on period, CBD increased wakefulness and decreased REM sleep. However, no changes in behavioral state were observed when CBD was given during the light-off phase. Anandamide alone increased TST. Yet, when both substances were given simultaneously, the arousing effects of CBD predominated and TST was decreased. CBD administration was also associated with an enhancement of c-Fos expression in the medial preoptic nucleus (MPO) of the hypothalamus, the dorsomedial hypothalamic nucleus and the dorsal raphe nucleus (DRD) of the brainstem. Extracellular levels of dopamine, noradrenaline and serotonin in the
nucleus accumbens were significantly increased, and 3,4-dihydroxy-L-phenylalanine (L-DOPA) and 5-hydroxy-indoleaceticacid (5-HIAA) levels were reduced.

C-Fos expression is believed to be a marker of neuronal activation. It was increased in the medial preoptic nucleus and dorsal raphe nucleus, areas which have been associated with waking (e.g. Lin et al., 1989; Jones, 2003). Elevated extracellular dopamine concentrations in the nucleus accumbens have also been related to waking (Lena et al., 2005).

The study does not contain any obvious biases.

Dosage differences may explain the deviating findings compared to the previous study. The dose was about 1000 times higher in the study by Monti (1977), yet it was injected intraperitoneally in contrast to the intracerebroventricular administration in the present study. According to the metabolism, penetrability and distribution of CBD in the rat brain (Alozie et al., 1979), and assuming a brain weight of about 1.5 g, the dosage would still be roughly 30 times higher in the previous than in the present study.

### 3.2.4.3. Studies measuring objective sleep effects of cannabis in humans

**Sleep effects of cannabis upon polysomnographically monitored sleep**

The total sample of all studies that examined the sleep effects of cannabis by using PSG comprised 129 subjects. The majority of these had prior experience with marijuana (see Tables 33a and 33b).

<table>
<thead>
<tr>
<th>Publication</th>
<th>Purpose of study</th>
<th>Subjects</th>
<th>Study design, administration protocol and outcome measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gillin et al., 1972</td>
<td>sleep effects of Δ-9-THC in depressive patients</td>
<td>3 psychiatric patients, age 46-61</td>
<td>DB, non-randomized, controlled trial 2 adaptation nights, 3 d placebo, 5-7 d 300µg/kg Δ-9-THC 2X/d, 2 d placebo</td>
<td>decrease in total REM sleep on first drug night</td>
</tr>
<tr>
<td>Kales et al., 1972</td>
<td>effects of marijuana administration and withdrawal upon REM sleep</td>
<td>4 naïve subjects, 4 chronic marijuana users, age and sex not given</td>
<td>non-randomized, controlled trial naïve subjects: 16-d study; smoking of marijuana on nights 5-7 and 12-14, placebo on remaining nights, chronic users: marijuana smoking on nights 1-4, withdrawal on nights 5-9, (n=2 with additional 4 d withdrawal, 3 d marijuana smoking, 2 d withdrawal)</td>
<td>decrease in REM sleep, fast development of tolerance, moderate REM rebound upon withdrawal</td>
</tr>
<tr>
<td>Pivik et al., 1972</td>
<td>sleep effects of acute Δ-9-THC and of synhex</td>
<td>4 young adult male volunteers, 2 different young adult male volunteers in the REM deprivation arm</td>
<td>DB, non-randomized, controlled trial oral administration of placebo or 4-17 mg Δ-9-THC at ‘lights-off’ baseline, drug and post-drug PSG recordings, REM deprivation arm: 5 baseline recordings, 2 nights of arousals, then oral administration of 20 mg Δ-9-THC or 60 mg of synhex, 5 nights of undisturbed sleep</td>
<td>Increase in TST, post-drug nights: increase in TST, decrease in REM sleep latency, REM deprivation study: REM rebound suppressed by cannabinoids</td>
</tr>
<tr>
<td>Freemont, 1972</td>
<td>sleep effects of acute Δ-9-THC and abstinence</td>
<td>2 female volunteers, age 23, infrequent marijuana use</td>
<td>DB, non-randomized, controlled trial 1 adaptation night, 1 baseline night, 4 drug nights, 2 follow-up nights immediately prior to lights-off, oral administration of placebo or 20 mg Δ-9-THC</td>
<td>Drug nights: decrease in REM%, withdrawal: increase in wakefulness, sleep onset REM period in one subject on 2nd recovery night</td>
</tr>
<tr>
<td>Hosko et al., 1973</td>
<td>sleep effects of acute Δ-9-THC</td>
<td>7 male volunteers, age 24-28, 3 regular marijuana users, 1 heavy user</td>
<td>SB, non-randomized, controlled trial 4 experimental nights, 2 nights without intervention, 3 experimental nights, oral administration of 200 µg/kg Δ-9-THC at 6 P.M. on night 3 or 4 and of 300 µg/kg Δ-9-THC on night 6 or 7</td>
<td>No consistent sleep alterations for group as a whole, in 2 subjects, increase in SWS and reduction in REM% (mainly higher dose), 1 subject with increase in REM% (after higher dose)</td>
</tr>
</tbody>
</table>

Table 33a: PSG studies investigating the effects of cannabis administration and withdrawal in humans
<table>
<thead>
<tr>
<th>Publication</th>
<th>Purpose of study</th>
<th>Subjects</th>
<th>Study design, administration protocol and outcome measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pranikoff et al., 1973</td>
<td>sleep effects of marijuana smoking and abstinence in chronic users</td>
<td>• 30 male almost daily marijuana users&lt;br&gt; • age 20-25&lt;br&gt; • 30 age-matched controls</td>
<td>• open, non-randomized, controlled trial&lt;br&gt; • before bedtime, n=10 users smoked marijuana until reaching a &quot;high&quot;&lt;br&gt; • n=20 users abstained from marijuana (for 24-36 h)&lt;br&gt; • PSG recordings 2 or 3 nights, first night as adaptation</td>
<td>• less stage 4 sleep in users who smoked before bedtime compared to controls&lt;br&gt; • more stage 2 and less stage 4 sleep in smokers compared to abstinent users</td>
</tr>
<tr>
<td>Barratt et al., 1974</td>
<td>effects of repeated administration of marijuana upon SWS</td>
<td>• 12 male experienced marijuana users&lt;br&gt; • age 21-26</td>
<td>• SB, non-randomized, controlled trial&lt;br&gt; • 1 adaptation night, 3 nights baseline, 10 drug nights, follow-up on nights 1,4,7&lt;br&gt; • controlled smoking of placebo (n=4) or 2 marijuana cigarettes (1.6% ∆-9-THC; n=8)&lt;br&gt; 2 h before lights-off</td>
<td>• acute administration: increase in SWS&lt;br&gt; • chronic administration: decrease in SWS&lt;br&gt; • follow-up nights: decrease in SWS</td>
</tr>
<tr>
<td>Feinberg et al., 1975</td>
<td>sleep effects of repeated high doses of ∆-9-THC and abstinence in chronic users</td>
<td>• 7 male daily marijuana users&lt;br&gt; • mean age 25&lt;br&gt; • only n=4 data available for all phases</td>
<td>• SB, non-randomized, controlled trial&lt;br&gt; • continuous hospitalization&lt;br&gt; • oral administration at 8 A.M., 12 P.M., 6 P.M., 9 P.M., between 10 and 11 P.M. and 4 A.M. of placebo during first week, of ∆-9-THC for 70 mg/d total, then increased to 210 mg/d, maintained for 12-16 d, then placebo</td>
<td>• increase in stage 4 sleep, decrease in REM sleep and REM density&lt;br&gt; • withdrawal: increase in SOL, decrease in TST&lt;br&gt; • decrease in total SWS&lt;br&gt; • decrease in REM latency, increase in total REM time and REM density</td>
</tr>
<tr>
<td>Feinberg et al., 1976</td>
<td>sleep effects of repeated high doses of marijuana extract and abstinence in chronic users</td>
<td>• 4 male marijuana users&lt;br&gt; • mean age 25.6&lt;br&gt; • only n=2 data available for all phases</td>
<td>• SB, non-randomized, controlled trial&lt;br&gt; • same protocol as in previous study&lt;br&gt; • oral administration of marijuana extract, containing same amount of ∆-9-THC as in previous study&lt;br&gt; • additionally, sleep data available for initial high dose (nights 9-11) and late withdrawal (nights 30-32)</td>
<td>• low dosage: decrease in REM density, increase in stage 4 sleep&lt;br&gt; • late high dosage: decrease in TST&lt;br&gt; • initial withdrawal: increase in SOL and in SWS%</td>
</tr>
<tr>
<td>Tassinari et al., 1976</td>
<td>effects of a single high dose of ∆-9-THC and hashish in naive subjects</td>
<td>• group A: 7 drug-naive volunteers&lt;br&gt; • ages 21-25&lt;br&gt; • group B: sleep recordings: 1 experienced marijuana user</td>
<td>• open, non-randomized study&lt;br&gt; • oral administration of 0.7-1.0 mg/kg ∆-9-THC between 7 and 9 P.M. (group A), or 1.4mg/kg hashish between 3 and 5 P.M. (sleep study subject group B)&lt;br&gt; • habituation night, 1 or 2 baseline nights (group A), drug night, 0-3 follow-up nights</td>
<td>• group A: increase in stage 2 sleep, decrease in REM sleep&lt;br&gt; • decrease in SOL (NS)&lt;br&gt; • group B: participant slept from 8 A.M. to 12 P.M. only in stage 2</td>
</tr>
<tr>
<td>Karacan et al., 1976</td>
<td>sleep patterns of chronic marijuana users</td>
<td>• 32 male chronic marijuana users&lt;br&gt; • mean age 30&lt;br&gt; • 32 controls</td>
<td>• cross-sectional study&lt;br&gt; • outpatient study&lt;br&gt; • 8 consecutive nights of sleep&lt;br&gt; • apparently no EMG recordings</td>
<td>• increased SOL&lt;br&gt; • greater REM%</td>
</tr>
<tr>
<td>Fremon, 1982</td>
<td>effects of repeated doses of ∆-9-THC and abstinence on sleep</td>
<td>• 2 brothers&lt;br&gt; • ages 23 and 25&lt;br&gt; • previous use of marijuana</td>
<td>• DB, cross-over, controlled trial&lt;br&gt; • administration of placebo just prior to lights-off on nights 1 through 23 for subject K (control series)&lt;br&gt; • for subject J, oral administration of 30mg ∆-9-THC on nights 6-19&lt;br&gt; • no medication on nights 24-27 and on 5 follow-up nights&lt;br&gt; • after 1 year cross-over&lt;br&gt; • subjective ratings of sleep every morning</td>
<td>• acute administration: increased WASO and decreased REM sleep&lt;br&gt; • chronic administration: decreased SWS%&lt;br&gt; • abstinence: increased SOL, increased WASO and decreased SWS%&lt;br&gt; • subjective sleep quality not affected</td>
</tr>
<tr>
<td>Nicholson et al., 2004</td>
<td>sleep effects of acute THC alone and in combination with CBD</td>
<td>• 8 volunteers&lt;br&gt; • 4 female (mean age 22)&lt;br&gt; • 4 male (mean age 29)&lt;br&gt; • prior occasional marijuana use</td>
<td>• DB, cross-over, controlled study&lt;br&gt; • 1 adaptation night, 4 experimental nights, each separated by 1 wk interval&lt;br&gt; • administration (oromucosal spray) of placebo, 15 mg THC, 5 mg THC+CBD, 15 mg THC+CBD from before 10:30 P.M.&lt;br&gt; • subjective assessments of sleep, sleepiness as well as sleep latency test in the morning&lt;br&gt; • various measures of performance and memory at about 9-10 A.M.</td>
<td>• decrease in total stage 3 sleep (5 mg THC+CBD and 15 mg THC+CBD)&lt;br&gt; • no change in subjective sleep quality&lt;br&gt; • next morning: increase in sleepiness after rising, mood decreased (both 15 mg THC and 15 mg THC+CBD), word recall compromised (15 mg THC), improvement in reaction time (5 mg THC+CBD)</td>
</tr>
</tbody>
</table>

Table 33b: PSG studies examining the effects of cannabis administration and withdrawal in humans
The abstract by Gillin et al. (1972) reports about a PSG study in three male psychiatric inpatients (ages 46 to 61). One was a psychotic depressive and the other two were manic-depressives. Nothing is stated about their prior experience with marijuana or current medication. After two adaptation nights, the patients received placebo for three days, presumably per os, then Δ-9-THC for five to seven days and again placebo for two days. Δ-9-THC was administered at 9 A.M. and 10 P.M. at a dose of 300 µg/kg each. PSG recordings were obtained on all of these nights. The only statistically significant change was a decrease in total REM sleep on the first drug night. After ingestion of Δ-9-THC, SOL appeared to be increased. The limitations of this study are obvious. Aside from the small sample size and the lack of detailed information on the study design, it needs to be held in mind that the participants of this study were all psychiatric patients. Sleep, and in particular REM sleep, is disturbed markedly in affective disorders.

Four marijuana-naïve subjects and four chronic marijuana users participated in the study by Kales et al. (1972). The results were published in the form of an abstract which does not provide any further description of these individuals. The drug-naïve participants smoked placebo-marijuana on the first four nights, followed by three nights of marijuana smoking, four nights of placebo, three nights of active marijuana and another two nights of placebo. The experienced users smoked marijuana on the first four nights. In two subjects, this was followed by five withdrawal nights. For the other two users, the abstinence period lasted nine nights, and they had three additional nights of marijuana smoking and two more withdrawal nights. In both subgroups of the study, marijuana smoking resulted in a decrease in REM sleep. Tolerance to this effect developed quickly, and REM sleep was even increased in a non-specified number of drug-naïve subjects after repeated drug administration. A moderate REM rebound was observed during marijuana withdrawal in both subgroups.

The abstract provides very insufficient data. Number of marijuana cigarettes smoked and Δ-9-THC content, time of administration, what substance served as placebo, sleep continuity and NREM sleep measures as well as statistical analyses are not reported. This makes a comparison with other studies difficult.

Pivik et al. (1972) studied the sleep effects of Δ-9-THC and of a semi-synthetic Δ-6α-10-THC homologue called synhexl. Participants were four young adult males, who had not used drugs for two months prior to the experiments, but whose drug histories are not further specified. They were administered, in a double-blind manner, placebo or a marijuana extract containing 17, 13, 8.6 or 4.3 mg Δ-9-THC orally at “lights-off”. PSG tracings were registered during baseline, on drug nights and on follow-up nights. There was an interval of at least two months between interventions. TST was significantly increased. For the 17 mg dose level, stage 2 sleep was decreased during the first half of the night, and increased during the second portion. There was a trend for an increase in stage 4 sleep during the first half of the night. This finding was most pronounced for the 17 mg dose. REM sleep decreased significantly during the second half of the nights at the 13 and 17 mg dose levels. During the first post-drug night, TST was increased. Stage 1 sleep was reduced at the 17 mg
Δ-9-THC dose level. SWS apparently shifted to the second half of the night. REM sleep increased during the first half of the night at the 17 mg Δ-9-THC dose level and REM sleep latency decreased.

Two different young adult male volunteers participated in the REM deprivation arm of the study. This procedure was performed in order to obtain additional information on the REM-reducing effects of the tetrahydrocannabinols. It was examined whether these substances were capable of suppressing the REM rebound that is usually observed after REM sleep deprivation. In the mornings after each of two separate nights of arousals, which were performed by one of three different REM deprivation procedures, 20 mg Δ-9-THC or 60 mg synhexl were given orally. Five nights of undisturbed sleep and without further drug administration followed. The sleep patterns after the third REM deprivation procedure, where no active drug was given, served for control values.

After administration of the cannabinoids, no statistically significant REM rebound was observed. Yet, an REM rebound occurred when no active drug was administered. There was an increase in stage 4 sleep during recovery nights after Δ-9-THC, however the statistical significance of this finding is not clear.

The trial was designed to examine the effects of Δ-9-THC. However, in fact, a marijuana extract was administered, and the doses of other cannabinoids in the extract were not quantified.

In a letter to the editor, Freemon (1972) reports about a double-blind study in which placebo or 20 mg Δ-9-THC was administered orally to two female volunteers, 23 years of age. The participants had infrequent prior experience to the drug. The first night on placebo served as a baseline recording, whereas on the subsequent four nights, active Δ-9-THC was given prior to bedtime. Two consecutive follow-up recordings with ingestion of placebo served as a “withdrawal” phase. No statistical analyses were performed.

On the four drug nights, REM sleep percentage was decreased from a mean of 25.4% at baseline to a mean of 18.7%. No data are provided on the sleep stages of NREM sleep. Upon discontinuation of Δ-9-THC, SOL and WASO were increased. On the second recovery night, one volunteer had a sleep onset REM period, REM sleep latency was only 6 minutes. Mean REM sleep percentage was 23% for the two recovery nights.

The most important limitations of this study are the small sample size, the lack of information on study design and characteristics of the participants as well as the absence of statistical analyses.

Hosko et al. (1973) administered Δ-9-THC single-blind to seven male volunteers, aged between 24 and 28 years. Among these, there were three regular and one heavy marijuana users. 200 µg/kg Δ-9-THC was given orally at 6 P.M. on one of four consecutive experimental days, and placebo was ingested on the other nights. Participants had no interventions for the two days of the weekend. They returned for the administration of 300 µg/kg Δ-9-THC (400 µg/kg Δ-9-THC in one subject) on one of the two following experimental sessions. In addition to PSG recordings, subjective feelings, vital signs, reflexes, equilibrium and reaction time were also assessed. Sleep stages were examined differentially for each half of the night. It is not clear whether statistical analyses were carried out.

After ingestion of Δ-9-THC, participants felt “strange”, pulse rate was increased and hyperreflexia was noted. Blood pressure remained unchanged. No significant alterations of sleep patterns were
observed for the group as a whole. In two subjects, there was an increase in SWS and a reduction in REM sleep percentage after Δ-9-THC ingestion, followed by an REM rebound upon recovery. One subject had an increase in REM sleep percentage after the higher dose of Δ-9-THC.

The group was very heterogeneous with respect to prior use of marijuana. This might explain the lack of a consistent pattern of sleep effects.

Sleep patterns of almost daily marijuana users after smoking and during abstinence were examined by Pranikoff et al. (1973). 30 male chronic marijuana users (ages 20 to 25) were compared to 30 age-matched controls. All participants reported to the laboratory for recordings shortly before bedtime. After an adaptation night, ten users smoked marijuana until they reached a subjective “high” immediately prior to bedtime, and 20 users abstained from marijuana. This amounted to a total of 24 to 36 hours of abstinence from marijuana. Some participants in the abstinence arm spent an additional night in the laboratory. No intervention was performed in control subjects.

Marijuana subjects who consumed cannabis prior to bedtime had a significantly lower stage 4 percentage compared to healthy controls. Not achieving statistical significance, REM sleep percentage was reduced. There were no significant differences between abstaining users and healthy controls. Stage 4 percentage was relatively high in abstainers (16%). When both groups of cannabis users were compared, marijuana smoking increased SOL and stage 2 sleep and it decreased stage 4 sleep.

An objective confirmation of abstinence from psychoactive drugs, including marijuana, would have been necessary in this study. Marijuana purity and amount of intake were not standardized objectively in the “smoking” arm of the study. Placebo was not administered to control subjects, hence psychological and nicotine effects of smoking prior to bedtime were not accounted for. Total time in bed was not standardized and varied greatly among subjects. The comparison between abstainers and users appears to have been introduced only ex post, and group sizes differed importantly.

The effects of repeated smoking of marijuana upon sleep were investigated by Barratt et al. (1974). Twelve male experienced marijuana users (ages 21 to 26) participated in this study. The extent of prior marijuana usage is not specified. After an adaptation night, subjects reported to the laboratory in the evenings of three baseline nights, ten drug nights and on follow-up nights 1, 4 and 7. On drug nights, eight subjects smoked two marijuana cigarettes containing 1.6% Δ9-THC according to a standardized technique. This amounted to an estimated total of 0.2 mg/kg Δ9-THC. The other four participants received cigarettes containing alfalfa placebo. Subjects went to bed at 10 P.M. Only the last two days of baseline were included in the statistical analyses. A chi-square test for the direction of change in sleep stages was performed for the total of 80 drug nights of the subjects receiving marijuana. Wilcoxon's test for nonpaired replicates compared sleep stage percentages of drug and post-drug nights with baseline values of each subject.

On the first drug night, both the experimental and the control group had a lower TST and a lower REM sleep percentage compared to baseline. In the experimental group, SWS was increased during the first four drug nights. This was followed by a significant decrease in SWS on drug nights 8 to 10 and on the recovery nights. Stage 2 sleep changed in the opposite direction, without achieving statistical
significance. Total body movements were decreased on drug nights 3 to 5 and during recovery, but increased on drug night 8. There were no further statistically significant changes.

The “lights-off” time was early (10 P.M.) and different from common habits of young adults. PSG recordings during all seven consecutive follow-up nights would have been more adequate. The statistical methods employed by the investigators presuppose independent variables, however subsequent nights of the same subject are not independent.

A study by Feinberg et al. (1975) examined the sleep effects of repeated high doses of Δ-9-THC in experienced users. Seven male marijuana users (mean age 25), who smoked 1 to 2 marijuana cigarettes per day, participated in this inpatient study. Placebo was administered orally at 8 A.M., 12 P.M., 6 P.M., 9 P.M., just prior to sleep and at 4 A.M. during the first week. Then, Δ-9-THC was ingested single-blind at these time points adding up to a total of initially 70 mg Δ-9-THC daily, being increased to 210 mg daily within 2 to 5 days. This high dose was maintained for 12 and 16 days, before placebo was reinstituted. Some subjects smoked a single marijuana cigarette on baseline and withdrawal days. Behavioral measures, waking EEG and sensory evoked potentials were obtained. Since sleep studies were only included after the beginning of the study, PSG recordings were performed during all phases only in four subjects. Recordings were obtained during three baseline nights, three nights on 70 mg Δ-9-THC, the last three nights on 210 mg Δ-9-THC and the first three nights of abstinence. The other three participants supplied data only for the high dosage and withdrawal phases.

Ingestion of the high dose of Δ-9-THC was associated with sedation, but after 5 to 6 days, tolerance developed to this effect. There was a significant decrease in total REM sleep, REM density and total number of eye movements during the 70 mg condition. When individuals were run on the long-term high dosage, total REM sleep continued to be decreased significantly. SOL increased from 14 minutes at baseline to 32 minutes (NS). The first SWS period was significantly shorter than the second and third. Total stage 3 sleep was decreased, but stage 4 percentage was increased significantly compared to the lower dose condition. Upon withdrawal, participants were more alert and somewhat more irritated. TST was decreased due to an increase in SOL. There was a decrease in total SWS and in stage 3 sleep alone. REM sleep latency was decreased, and total REM sleep, REM sleep percentage and, even more pronounced, REM density were increased. Notably, the first REM sleep period was unusually long.

The sample size for the full protocol was small. The disturbing awakening at 4 A.M. is an unrealistic detail. The baseline data may have been superposed by residual or withdrawal effects from cannabis and alcohol use. Also, the aforementioned use of cannabis in addition to the study protocol by some individuals may have altered the sleep recordings during baseline and abstinence. The data for late high dosage are difficult to interpret, since they combine effects of chronic administration with effects of increasing doses.

The same investigators carried out a similar study with marijuana extract (Feinberg et al., 1976). Four male marijuana users (mean age 25.6) participated in this month-long inpatient study. Only two provided data for all phases. Instead of the 96%-pure Δ-9-THC used in the previous study, the
investigators orally administered a marijuana extract containing the same amount of Δ-9-THC (29% of the extract), but also 1.5% cannabinol and 2.8% CBD. Moreover, a second difference from the first experiment was that PSG recordings were also obtained for the initial high dose and for withdrawal days 9 to 11 in two subjects.

When marijuana extract containing a daily total of 70 mg Δ-9-THC was administered, stage 4 percentage was increased and REM density decreased. There was a non-significant decrease in SOL. During the initial high dose condition, the number of awakenings was increased and total eye movements were reduced. During late high dosage, total time awake was increased and, accordingly, TST was decreased. This was in particular due to an increase in the average duration of awakenings. Upon withdrawal, SOL (only compared to initial high dosage), stage 3 percentage of TST and SWS percentage were increased. During the second week of abstinence, a decrease in stage 2 percentage and an increase in SWS percentage were increased. During the second week of abstinence, a decrease in stage 2 percentage and an increase in SWS percentage were statistically significant compared to baseline.

The results of this study were similar to the previous one. However, owing to the even smaller sample size, it was more difficult for findings to reach statistical significance. On the whole, the two studies by Feinberg et al. (1975, 1976) were well-conducted.

The investigators also collapsed the data from all individuals of the two studies. One has to bear in mind that this is not entirely legitimate, since subjects of the second study also ingested CBD. Stage 3 percentage appears to decrease after ingestion of cannabis, but stage 4 sleep increases. Furthermore, REM sleep, REM density and total number of eye movements are decreased. During initial withdrawal, there is an increase in SOL and WASO and a reduction in TST. Moreover, an REM rebound is observed: REM sleep latency is decreased and total REM sleep and REM density are increased.

A single high dose of Δ-9-THC or hashish was administered to drug-naïve subjects in the study by Tassinari et al. (1976). In the THC group, seven drug-naïve volunteers, aged 21 to 25, received 0.7 to 1.0 mg/kg Δ-9-THC orally between 7 and 9 P.M. The sleep study subject from the hashish group was a weekly marijuana user. He was given 1.4 mg/kg hashish orally between 3 and 5 P.M. There was no blinding in either group. After a habituation night, there were 1 to 2 control nights followed by the experimental night and 0 to 3 follow-up nights in the laboratory. In addition to PSG recordings, the neuropsychiatric symptomatology including vital signs, mood, psychomotor activity and deep tendon reflexes, was assessed.

After drug ingestion, participants became tachycardic and then developed dysphoric symptoms and anxiety, abnormal movements and hyperreflexia. This was followed, 2 to 3 hours after intake, by a state of drowsiness which led to sleep. Volunteers from the THC group had an increase in stage 2 sleep and a non-significant decrease in SWS. REM sleep was suppressed almost completely. On the post-drug nights, there was a non-significant REM rebound and measures returned to baseline values. The subject who received hashish did not fall asleep until 8 A.M. and slept until 12 P.M. Neither SWS nor REM sleep were observed, he spent the entire sleep period in stage 2 sleep. Two volunteers experienced severe panic attacks and tried to escape from the laboratory. One subject reached the main street naked. His panic attack was associated with hallucinations and paranoid ideation. This was 90 minutes after he received an oral dose of 0.9 mg/kg Δ-9-THC.
The most obvious limitation of this study is the lack of blinding and of a control group. Therefore, the expectations of a drug intoxication experiment, which apparently played an important role, were not controlled for.

Karacan et al. (1976) examined the sleep patterns of 32 male chronic marijuana users (mean age 30.3 years) in Costa Rica. They smoked a mean of 9.2 marijuana cigarettes per day, ranging from 2.5 to 23. 32 matched non-users (mean age 30.4) served as control subjects. Sleep EEG recordings, apparently without EMG tracings, were obtained during eight consecutive nights of sleep. In the morning, subjects filled out a sleep questionnaire, but the results are not presented in the article. The investigators attempted to prevent subjects from smoking marijuana during the last two hours before bedtime, from drinking coffee or tea after 5 P.M., from napping during the daytime and from using alcohol. However, these instructions could not be enforced.

Chronic marijuana users had a significantly higher REM sleep percentage than controls. This was due to a longer average duration of REM sleep periods. There were trends for an increased SOL, reduced SE and increased total time in bed in marijuana users.

The extent of marijuana smoking during the daytime was not standardized, and the mean habitual dose varied substantially. It is possible that acute withdrawal effects influenced the sleep recordings. Since comorbid psychiatric problems were not assessed, it cannot be ruled out that e.g. depression contributed to the elevated REM measures. Apparently no EMG recordings were obtained and sleep stage definition was not according to standard criteria (Rechtschaffen and Kales, 1968). Moreover, the altered sleep patterns observed in this study are not necessarily an effect of drug consumption. They may have existed already before onset of drug abuse, e.g. as a predisposing characteristic.

Two brothers aged 23 and 25, with previous usage of marijuana, participated in the double-blind, cross-over study by Freemon (1982). Subject K received oral placebo on all 23 drug nights, whereas subject J was given 30 mg ∆-9-THC orally just prior to "lights out" on nights 6 to 19. No drug was given on nights 24 to 27 or on the follow-up nights 32 to 35. After one year, this protocol was alternated. Subjective sleep quality was assessed every morning, using a scale from 1 to 7. PSG recordings were obtained on all aforementioned nights. Values more than twice the standard deviation from the average of the control period were considered statistically significant.

Subject J had a significantly increased WASO and decreased REM percentage during his first night on ∆-9-THC. SWS percentage was decreased on the 6th and 9th night on ∆-9-THC for subject J, and on the 7th and 8th night for subject K. Hence, repeated administration of ∆-9-THC may decrease SWS. During the subsequent phase of abstinence, SOL was increased on the second night for subject J and on the first for subject K. WASO was increased significantly on five different nights for subject J and on two nights in subject K. SWS percentage was decreased on three different nights in subject J and on six nights for subject K. REM sleep percentage was increased on night 14 of discontinuance for subject J. The subjective estimates of overall sleep quality was not reduced during withdrawal.

The calculated mean values for each condition are shown in Tables 34a and 34b. Only the eight consecutive recovery nights are considered. The tables indicate that REM sleep is decreased during the drug administration phase only in subject J. Moreover, it suggests an increase in wakefulness and
a reduction in SWS percentage during withdrawal. It is not clear why the 27-day control series differ from the 5-day pre-drug conditions in some measures.

The study is limited by the small sample size (n=2). No recordings were carried out between nights 8 and 13 of discontinuance.

<table>
<thead>
<tr>
<th>Subject J</th>
<th>Total time awake</th>
<th>SWS%</th>
<th>REM%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control series</td>
<td>28.3 min</td>
<td>17.6%</td>
<td>19.6%</td>
</tr>
<tr>
<td>Pre-drug (5 d)</td>
<td>21.0 min</td>
<td>14.2%</td>
<td>19.8%</td>
</tr>
<tr>
<td>30 mg Δ-9-THC (14 d)</td>
<td>22.1 min</td>
<td>15.3%</td>
<td>15.9%</td>
</tr>
<tr>
<td>Abstinence (8 d)</td>
<td>44.3 min</td>
<td>13.3%</td>
<td>20.8%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subject K</th>
<th>Total time awake</th>
<th>SWS%</th>
<th>REM%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control series</td>
<td>7.1 min</td>
<td>26.2%</td>
<td>21.8%</td>
</tr>
<tr>
<td>Pre-drug (5 d)</td>
<td>4.6 min</td>
<td>26.4%</td>
<td>21.6%</td>
</tr>
<tr>
<td>30 mg Δ-9-THC (14 d)</td>
<td>4.4 min</td>
<td>24.1%</td>
<td>22.4%</td>
</tr>
<tr>
<td>Abstinence (8 d)</td>
<td>9.0 min</td>
<td>18.9%</td>
<td>20.3%</td>
</tr>
</tbody>
</table>

Tables 34a and 34b: Mean values for subjects J and K during each phase of the experiment (Freemon, 1982)

Nicholson et al. (2004) administered Δ-9-THC alone and in combination with CBD in doses relevant for therapeutical use as analgesics. Eight volunteers (ages 21 to 34 years; 4 female) with prior occasional use of marijuana participated in this double-blind, cross-over study. After an adaptation night, there were four experimental nights, each separated by a one-week interval. Breath alcohol levels and urine toxicology screens were obtained on each treatment night. 15 mg THC, 5 mg THC in combination with 5 mg CBD, 15 mg THC in combination with 15 mg CBD or placebo were administered by means of an oromucosal spray between 10:00 and 10:30 P.M. Bedtime was at 11 P.M. In addition to PSG recordings, measures of subjective sleep quality, subjective sleep quantity and of sleepiness upon rising were rated with visual analog scales and the Stanford Sleepiness Scale, respectively. Mood, performance, memory and, again, sleepiness were assessed between 9 and 10 A.M., and a sleep latency test was performed.

For the 15 mg THC condition, there was a trend for an increased REM sleep latency. Sleepiness after rising was increased and wakefulness on the visual analog scale was diminished. Immediate and delayed verbal recall were significantly compromised. Mood ratings were decreased. The sleep latency test at 10 A.M. demonstrated a reduced SOL in the morning.

After administration of 5 mg THC and 5 mg CBD, total stage 3 sleep decreased significantly. Reaction time improved the next morning.

When 15 mg THC was given in combination with 15 mg CBD, stage 3 sleep decreased, and wakefulness tended to be increased. Sleepiness was increased and wakefulness was reduced upon rising. Mood ratings were decreased. Fatigue and sleepiness were increased at 10 A.M.

There were no changes in subjective sleep quality. No serious adverse effects were reported.

The study was conducted very well. Residual drug effects the morning after drug administration would be expected to be more prominent in older individuals.
Studies assessing effect of Δ-9-THC upon objective measures of sleep other than PSG

There are two studies that assessed objective measures of sleep, yet did not employ PSG. They confirm the sedative properties of cannabis (see Table 35).

<table>
<thead>
<tr>
<th>Publication</th>
<th>Purpose of study</th>
<th>Subjects</th>
<th>Study design, administration protocol and outcome measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cousens and DiMascio, 1973</td>
<td>Δ-9-THC as hypnotic in insomniacs</td>
<td>9 male, physically healthy insomniacs, ages 21-40, prior use of marijuana</td>
<td>DB, cross-over, placebo-controlled study, sleep laboratory 1X/wk for 6 wk, 2 wk adaptation, oral administration of 10 mg, 20 mg, 30 mg of Δ-9-THC and placebo on the following 4 occasions, data collected by one sleep observer</td>
<td>decrease in total time to fall asleep (20 mg the most effective)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>no significant differences for &quot;time to bed&quot; and &quot;time to fall asleep after going to bed&quot;</td>
</tr>
<tr>
<td>Walther et al., 2006</td>
<td>effect of Δ-9-THC on nocturnal motor activity in dementia</td>
<td>6 inpatients with dementia and associated nighttime agitation, mean age 81.5</td>
<td>open, non-randomized study, continuous recording of motor activity by means of an actometer, 2 d of baseline, Neuropsychiatric Inventory, oral administration of 2.5 mg Δ-9-THC at 7 P.M. for 2 wk, Neuropsychiatric Inventory repeated at end of treatment</td>
<td>no adverse events</td>
</tr>
</tbody>
</table>

Table 35: Studies in humans assessing sleep by means of a sleep observer or actigraphy

In the study by Cousens and DiMascio (1973), Δ-9-THC was administered to nine physically healthy males (ages 21 to 40) who reported mild insomnia with a SOL of 60 to 90 minutes. They had prior experience with marijuana, but were not abusing the substance at present. Participants spent one night per week in the sleep laboratory for six weeks. The first two weeks served for habituation. Then, 10, 20 or 30 mg of Δ-9-THC or placebo was given orally in a double-blind manner and in a random sequence. Sleep continuity data were collected by a single bedside observer. This was facilitated by the fact that the subjects’ beds were only separated by dividers. In the morning, a sleep questionnaire was filled out by each subject.

After administration of all doses of THC, volunteers had a significantly reduced total time to fall asleep. The 20 mg dose appeared to be the most effective (118 minutes versus 180 minutes after placebo). This measure was the sum of “time to bed after drug ingestion” and “SOL after going to bed”. The differences did not achieve statistical significance for either individual measure. Number of awakenings and WASO were not affected by the drug.

The study contains some specific weaknesses due to the lack of PSG recordings. The setting was uncomfortable, since all subjects had to sleep within the same room. The observations were not exact, because the sleep observer was only able to take notes on each individual once every 15 minutes.

The effects of Δ-9-THC upon nocturnal motor activity in severe dementia were assessed by Walther et al. (2006). Six consecutive inpatients with dementia accompanied by nighttime agitation, circadian rhythm disturbances or sundowning participated in the study. Their mean age was 81.5 years. Upon admission to the hospital, each patient’s motor activity was registered continuously by means of an actometer. This device is worn on the non-dominant arm and it detects and counts movements. According to Ancoli-Israel et al. (1997) and Mahlberg et al. (2004), wrist actigraphy is a valid method to
monitor sleep-wakefulness also in patients suffering from dementia. During the first two days of baseline and at the end of the experiment, the Neuropsychiatric Inventory was assessed. 2.5 mg of dronabinol (Δ-9-THC) was administered orally at 7 P.M. throughout the two-week treatment phase. Subjects were not blinded with respect to the administration protocol.

Nocturnal motor activity decreased significantly after administration of Δ-9-THC. This reduction was observed already after the first dose. The Neuropsychiatric Inventory total score improved across the experiment. Specifically, there were improvements in the subscores for aberrant motor behavior, agitation, nighttime behaviors, appetite disturbances and irritability. Furthermore, Δ-9-THC ingestion was associated with a trend for a decrease in anxiety. No adverse events were registered, and the amount of additional medication did not change.

The patients presented with important comorbidity and a broad spectrum of additional (also psychiatric) medication. Since there was no control group, effects of the continued hospitalization such as habituation to the new environment were not accounted for. Side effects upon cognition were not investigated systematically.

### 3.2.4.4. Studies assessing subjective sleep effects of cannabis

**Effects of acute cannabis administration upon subjective measures of sleep**

There are four studies that furnish some data upon the sleep effects of cannabis administration, without taking into consideration cannabis withdrawal (Cunha et al., 1980; Chait 1990; Chait and Zacny, 1992; Blake 2006; see Table 36).

<table>
<thead>
<tr>
<th>Publication</th>
<th>Purpose of study</th>
<th>Subjects</th>
<th>Study design, administration protocol and outcome measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cunha et al., 1980</td>
<td>anticonvulsant properties of CBD</td>
<td>• 16 healthy volunteers&lt;br&gt;• ages 22-35&lt;br&gt;• 15 epileptic patients&lt;br&gt;• age 14-49</td>
<td>• DB, randomized controlled trial&lt;br&gt;• ingestion of 2 capsules placebo or 1.5 mg/kg CBD (1 in morning and 1 in afternoon) for 30 d</td>
<td>side effects of CBD:&lt;br&gt; 8 healthy subjects: n=2&lt;br&gt; <strong>somnia</strong>, n=1 improvement of preexisting insomnia&lt;br&gt; 8 epileptic patients: n=4 somnolence</td>
</tr>
<tr>
<td>Chait, 1990</td>
<td>after-effects of marijuana smoking</td>
<td>• 12 regular marijuana smokers&lt;br&gt;• mean age 21</td>
<td>• DB, cross-over, placebo-controlled study&lt;br&gt;• smoking sessions at 3 P.M. (Sat and Sun) and at 9 P.M. (Fri through Sun)&lt;br&gt;• marijuana cigarettes with 0.0% Δ-9-THC one weekend and 2.1% Δ-9-THC the other&lt;br&gt;• sleep questionnaire, test battery in the morning</td>
<td>• greater ease in getting to sleep after Δ-9-THC&lt;br&gt; • no other significant differences&lt;br&gt; • no “hangover” syndrome</td>
</tr>
<tr>
<td>Chait and Zacny, 1992</td>
<td>oral Δ-9-THC and smoked marijuana as a reinforcer</td>
<td>• assessment of sleep in THC arm: 11 regular marijuana users&lt;br&gt;• age 22</td>
<td>• SB, non-randomized, placebo-controlled study&lt;br&gt;• THC arm: 2 trials of each 2 sampling sessions (Mo, Wed) and 1 choice session (Fri)&lt;br&gt;• on sampling sessions, oral administration of 10 mg (n=5) or 15 mg (n=6) Δ-9-THC or of placebo from 7:00 to 11:30 P.M.&lt;br&gt;• sleep questionnaire in the morning</td>
<td>no significant differences between drug and placebo in any items of sleep questionnaire</td>
</tr>
<tr>
<td>Blake et al., 2006</td>
<td>marijuana extract as analgesic in rheumatoid arthritis</td>
<td>• 58 patients with rheumatoid arthritis (31 Sativex, 27 placebo)&lt;br&gt;• mean age 62.8</td>
<td>• DB, randomized controlled trial&lt;br&gt;• administration of Sativex or placebo for 5 wk via oromucosal spray in evening (mean 14.6 mg Δ-9-THC, 13.5mg CBD daily)&lt;br&gt;• pain, morning stiffness and sleep quality assessed with numerical rating scale each morning</td>
<td>• improvement in pain on movement and at rest&lt;br&gt; • improvement in quality of sleep&lt;br&gt; • residual drowsiness reported not more frequently than under placebo</td>
</tr>
</tbody>
</table>

Table 36: Studies investigating subjective sleep effects of cannabis administration
Cunha et al. (1980) tested the anticonvulsant properties of CBD and its safety. Hence, the sleep effects of this agent were not the primary outcome measure of the study. Eight out of 16 healthy volunteers (ages 22 to 35) and 8 out of 15 epileptic patients (ages 14 to 49) received CBD. One epileptic patient was run on the CBD and the placebo schedule. 1.5 mg/kg CBD was ingested orally twice a day, in the morning and in the afternoon, for 30 days. Drug administration was double-blind, the other participants received placebo. The patients continued to take their habitual antiepileptic medication during the study. Adverse effects were registered, but not assessed systematically. The clinical condition of four of the 8 epileptic patients receiving CBD improved substantially, and another three patients improved partially. Seven of the 8 placebo patients did not improve, and one improved clearly. Four patients receiving CBD reported somnolence, compared to one out of the placebo epileptic patients. Out of the 8 healthy subjects who received CBD, two reported somnolence and one mentioned an improvement of preexisting insomnia. No alterations of sleep were cited by healthy controls receiving placebo. No serious side effects were observed. The effects of CBD upon sleep might be confounded by the additional medication of each patient. The actual ingestion of the CBD capsules was not confirmed objectively. The severity of somnolence was not quantified, and no statistical analyses were performed.

The after-effects associated with marijuana smoking were investigated in a double-blind, cross-over study by Chait (1990). Twelve regular marijuana smokers (mean age 21) participated in a single evening practice session and in two experimental weekends. Smoking sessions were at 9 P.M., but on Saturdays and Sundays additionally at 3 P.M. Marijuana cigarettes containing 0.0% Δ-9-THC were smoked on one weekend, whereas on the other, cigarettes contained 2.1% Δ-9-THC. Smoking was performed following a standardized puffing procedure. In the mornings, the Leeds Sleep Questionnaire was completed. Afterwards, mood, temporal perception and the subjects’ performance on reaction time, psychomotor function and cognitive tasks were assessed. After administration of Δ-9-THC, individuals reported a significantly greater ease in “getting to sleep” compared to placebo. No significant differences were observed on any other item of the Leeds Sleep Questionnaire. The mood questionnaires and the behavioral tasks yielded practically no evidence of residual intoxication effects.

The most striking bias of this paper is the fact that “placebo” marijuana contained all active marijuana constituents other than Δ-9-THC, i.e. notably considerable amounts of CBD. Moreover, there was no adaptation night in the laboratory.

Chait and Zacny (1992) examined whether oral Δ-9-THC and smoked marijuana served as a reinforcer in regular marijuana users. Only those volunteers who received Δ-9-THC in this study (mean age 22) filled out the Leeds Sleep Questionnaire in the morning. Eleven subjects were included in the analyses. There were two practice sessions and two trials of two sampling sessions and a choice session each. On sampling sessions, 10 mg of Δ-9-THC (n=5), 15 mg of Δ-9-THC (n=6) or placebo was administered orally from 7:00 to 11:30 P.M. On choice sessions, subjects decided to take one of the two colored capsules that they had received during the previous sampling sessions. In addition to the sleep questionnaire, mood and subjective effects were assessed.
Statistical analyses yielded no significant differences between drug and placebo in any of the items of the Leeds Sleep Questionnaire. Both oral Δ-9-THC and smoked marijuana were identified as positive reinforcers for self-administration. One individual quit the study due to a prolonged aversive response to Δ-9-THC.

The study does not contain any obvious biases. It is not clear why no sleep effects were noted.

The analgetic effects of a marijuana extract in rheumatoid arthritis were studied by Blake et al. (2006). Sleep effects were not the primary outcome measure. They were taken into consideration as part of the assessment of the drug’s tolerability. 58 patients with rheumatoid arthritis (mean age 62.8) were randomized to receive either placebo (n=27) or Sativex (n=31), a whole plant extract which contains roughly equal amounts of Δ-9-THC and CBD, as well as traces of minor cannabinoids. Placebo or Sativex were administered for five weeks by means of an oromucosal spray in the evening. Patients in the Sativex group received a daily mean of 14.6 mg Δ-9-THC and 13.5 mg CBD. Pain on movement and the secondary outcome measures pain at rest, sleep quality and morning stiffness were assessed by a numerical rating scale each morning.

Pain on movement and at rest was improved significantly in the Sativex group compared to placebo. A better sleep quality was reported. Drowsiness as a potential adverse effect was not reported more frequently than in the placebo group.

The study was well-conducted. However, it appears likely that the improved sleep quality was accounted for much less by the drug’s hypnotic properties than by its analgetic effects.

Changes in sleep effects of marijuana in chronic users

The changes in marijuana effects over the years were addressed in a cohort study by Halikas et al. (1985; see Table 37).

<table>
<thead>
<tr>
<th>Publication</th>
<th>Purpose of study</th>
<th>Subjects</th>
<th>Study design and outcome measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Halikas et al., 1985</td>
<td>changes in marijuana effects over years of use</td>
<td>97 Caucasian regular marijuana users (mean age at first interview 22)</td>
<td>cohort study, checklist of acute marijuana effects and after-effects in 1969/70 and again 1975-77, 105 items of commonly reported marijuana effects, frequency assessed by subjects as “once or never”, “occasional” or “usual”</td>
<td>decrease in desirable after-effects upon sleep (more restful sleep, waken refreshed, more sleep), no change in desirable acute effects upon sleep (drowsiness) or in undesirable after-effects (awaken tired, more dreams, fewer dreams, less restful sleep, less sleep)</td>
</tr>
</tbody>
</table>

Table 37: Studies assessing subjective sleep effects of chronic marijuana administration

97 Caucasian regular marijuana users (mean age 22 at the first interview) filled out a checklist of commonly reported marijuana effects in 1969/70 and again between 1975 and 1977. The checklist contained 105 items of acute effects and after-effects (“hangover” effects). Individuals marked each item depending on how frequently they experienced a particular effect (either “once or never”, “occasionally” or “usually”). Afterwards, the investigators formed groups of desirable and undesirable acute and after-effects, and the response to each item yielded a numerical value between 1 and 3. A
matched-pairs Wilcoxon ranked-signs test was then employed to identify changes in each category over the assessment period.

No data are given about the frequency of desirable and undesirable marijuana effects at baseline. Desirable acute effects upon sleep remained unchanged over the assessment period. This category only included the item “drowsiness”. There were no items in the category of undesirable acute effects upon sleep. Desirable after-effects upon sleep, such as “more restful sleep”, “waken refreshed”, “more sleep”, declined significantly by 1976. On the other hand, no changes in undesirable after-effects upon sleep, such as “awaken tired”, “more dreams”, “fewer dreams”, “less restful sleep”, “less sleep”, were noted. The same trends over time were observed for the categories of cognitive effects and mood effects.

The most obvious limitation of this study is the ex-post categorization of symptoms into desirable and undesirable. This blending together, although favoring statistical significance, impeded a distinct analysis. Furthermore, concomitant psychiatric disorders, use of other substances and preexisting sleep problems were not assessed. The study did not account for heterogeneity in the extent of marijuana usage.

Cross-sectional studies on the prevalence of sleep disturbances in cannabis withdrawal

Three surveys have examined the prevalence of sleep disturbances in marijuana users during cessation attempts (Wiesbeck et al., 1996; Budney et al., 1999; Vandrey et al., 2005; see Table 38).

<table>
<thead>
<tr>
<th>Publication</th>
<th>Purpose of study</th>
<th>Subjects</th>
<th>Study design and outcome measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wiesbeck et al., 1996</td>
<td>prevalence and clinical relevance of a marijuana withdrawal syndrome</td>
<td>• 5611 participants (758 alcohol-dependent, 4064 relatives, 789 controls)</td>
<td>• survey</td>
<td>• 14% of all frequent marijuana users reported sleep disturbance as a withdrawal symptom • 76% of those with withdrawal cluster reported sleep disturbance (2nd most frequent withdrawal symptom)</td>
</tr>
<tr>
<td>Budney et al., 1999</td>
<td>withdrawal symptoms in adult treatment seekers</td>
<td>• 54 treatment-seeking almost daily marijuana users, mean age 34</td>
<td>• survey • 22-item Marijuana Withdrawal Checklist during intake assessment, employed for most recent abstinence attempt</td>
<td>• 43% of patients with moderate to severe sleep problems • 37% moderate to severe strange dreams</td>
</tr>
<tr>
<td>Vandrey et al., 2005</td>
<td>withdrawal symptoms in adolescent treatment seekers</td>
<td>• 72 marijuana users (18 d/month), mean age 16</td>
<td>• survey • 15-item Marijuana Withdrawal Checklist during intake assessment, employed for most recent abstinence attempt</td>
<td>• 31% of patients with moderate to severe sleep difficulty (among 4 most frequent withdrawal symptoms • 18% moderate to severe strange dreams</td>
</tr>
</tbody>
</table>

Table 38: Studies on the prevalence of sleep disturbances in abstinent marijuana users

The sample of the study by Wiesbeck et al. (1996) consisted of 5611 participants (age not given), recruited through the Collaborative Study of the Genetics of Alcoholism. It included 758 alcohol-dependent patients (177 female), 4064 relatives of these probands (2430 female) and 789 control subjects (405 female). Data upon drug histories and problems associated with substance use were obtained through a semi-structured interview. Depending on their prior exposure to marijuana, the investigators divided all participants into four groups: 2300 subjects were marijuana-naïve, 1576 had
used marijuana, but not more frequently than on 20 occasions in a single year. Groups 3 and 4 had used marijuana at least 21 times in one year. The 1465 individuals from Group 3 denied ever having experienced two or more marijuana withdrawal symptoms at the same time when trying to cut down or stop marijuana use. The 270 subjects in Group 4 reported having had two of these symptoms clustering together. 98% of these latter subjects had a diagnosis of marijuana dependence. Based upon descriptions in the literature, the investigators had defined seven potential marijuana withdrawal symptoms: nervousness or irritability, sleep disturbance, appetite change, trembling or twitching, diaphoresis or fever, diarrhea, nausea or vomiting.

13.5% of all frequent marijuana users (Groups 3 and 4) reported disturbed sleep during abstinence from cannabis. However, this percentage was much higher among those who had experienced a withdrawal cluster (Group 4): 75.6% cited sleep disturbance as a withdrawal symptom. Sleep disturbance constituted the second most frequently reported withdrawal symptom.

The differences between Groups 3 and 4 may be explained by a number of facts: alcohol and other drug dependence as well as other DSM-III-R psychiatric diagnoses were prevalent, and their prevalence was significantly associated with groups. For instance, dependence on alcohol, cocaine, amphetamine, sedative/hypnotics and opiates, as well as antisocial personality disorder were most prevalent among probands in Group 4. In particular, groups 3 and 4 differed with respect to extent of marijuana usage. A logistic regression analysis revealed that sedative/hypnotics and alcohol dependence, antisocial personality disorder and extent of marijuana usage were significant predictors for experiencing a marijuana withdrawal cluster. The relatively low frequency of sleep disturbances when cutting down on or stopping marijuana use for all “frequent” marijuana users (i.e. 13.5%) may be a result of the low cut-off of only 20 times per year which was considered as “frequent” use. Those subjects who use cannabis slightly less than twice a month would not be expected to notice and report sleep disturbances upon “withdrawal”. The retrospective data collection (recall bias, in addition to a lack of focused attention on potential effects) may also have contributed to this relatively low percentage of sleep complaints.

Budney et al. (1999) examined marijuana withdrawal symptoms in a sample of 54 adults (mean age 33.8 years) who sought outpatient treatment for marijuana-related problems. Subjects, who were mostly daily users, completed the Marijuana Withdrawal Checklist during their intake assessment. The severity of 22 symptoms which are commonly reported during withdrawal from cannabis and other substances were rated for the subjects’ most recent abstinence attempt. Ratings were assigned numerical values between 0 and 3 (0=not at all; 3=severe).

67% of all participants reported having experienced sleep problems of any severity during their last cessation attempt. 43% reported moderate to severe sleep problems, and 37% moderate to severe strange dreams. They were among the eight most frequently experienced symptoms, after craving, irritability, nervousness, depression, restlessness and anger.

Co-use of other psychoactive substances, a possible reluctance to register or attribute symptoms to marijuana withdrawal and recall bias with respect to withdrawal symptoms and their intensity may have confounded the study’s results. When comparing study’s findings to group 4 of the study by Wiesbeck et al. (1996), it needs to be taken into consideration that the cited study asked about
abstinence symptoms during any prior cessation attempt. The percentages of marijuana-dependent subjects were similar (98% and 100%). In the study by Wiesbeck et al. (1996), 76% reported ever having experienced sleep problems during marijuana withdrawal. 67% reported disturbed sleep during their last abstinence attempt in the present study. Hence, the findings appear to be consistent.

A study similar to the one by Budney et al. (1999) was performed in adolescents (mean age 16.2) by Vandrey et al. (2005). Subjects were seeking outpatient substance use treatment, with marijuana being the primary substance of abuse. Mean frequency of use was only 18.1 days per month. A 15-item version of the Marijuana Withdrawal Checklist was filled out at the intake assessment. It investigated the presence and intensity of abstinence symptoms during subjects’ last attempt to discontinue marijuana usage.

Moderate to severe sleep difficulty was reported by 31% of the sample, constituting the fourth most important withdrawal symptom after craving, depression and irritability. 15% experienced moderate to severe strange dreams.

The same possible biases apply to this paper as to the previous one. The fact that prevalence and magnitude of marijuana cessation effects were lower in this study compared to those registered by Budney et al. (1999) may be explained by the lighter patterns of marijuana use in the present sample. Only 57% met DSM-IV criteria for cannabis dependence, compared to 100% in Budney et al. (1999). Mean frequency of cannabis use was 18 days per month, whereas the vast majority in the previous study smoked marijuana daily.

Studies investigating subjective sleep parameters in individuals withdrawing from marijuana

There is one case study and seven clinical trials on the cannabis withdrawal syndrome which also investigated the presence or absence and time course of sleep disturbances (see Table 39).
The first subject, male, 17 years of age, had a comorbid diagnosis of a conduct disorder and used treatment programs. All of them met criteria for cannabis dependence. The abstinence symptoms experienced by three adolescent heavy marijuana users are reported in the Table 39: Clinical studies assessing subjective sleep during marijuana withdrawal

<table>
<thead>
<tr>
<th>Publication</th>
<th>Purpose of study</th>
<th>Subjects</th>
<th>Study design, administration protocol and outcome measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duffy and Milin, 1996</td>
<td>withdrawal symptoms in adolescent heavy marijuana users</td>
<td>• 3 heavy, treatment-seeking marijuana users, ages 16-17</td>
<td>• case report of abstinence attempts</td>
<td>• within 24-48 h of abstinence, initial insomnia, no normalization before 10 d, abating later than other abstinence symptoms</td>
</tr>
<tr>
<td>Haney et al., 1999a</td>
<td>withdrawal symptoms after repeated oral THC</td>
<td>• 6 male, 6 female daily marijuana users, mean age 25</td>
<td>• SB, non-randomized, controlled study</td>
<td>• abstinence, subjective effects: decrease in “sedated”</td>
</tr>
<tr>
<td>Haney et al., 1999b</td>
<td>withdrawal symptoms after repeated smoked THC</td>
<td>• 12 male almost daily marijuana users, mean age 28</td>
<td>• SD between smoking and placebo, 4 d of 4X/d 5 puffs of 1.8% or 3.1%THC marijuana cigarettes, 4 d placebo, 4 d of other THC concentration, 4 d placebo</td>
<td>• no significant changes in sleep-related subjective effects or in the Saint Mary’s Hospital Sleep Questionnaire</td>
</tr>
<tr>
<td>Budney et al., 2001</td>
<td>clinical significance of marijuana withdrawal in outpatients</td>
<td>• 7 male, 5 female daily marijuana users, mean age 30</td>
<td>• open, non-randomized study</td>
<td>• during abstinence, decrease in sleep quality, increase in sleep difficulty, increase in strange dreams</td>
</tr>
<tr>
<td>Budney et al., 2003</td>
<td>withdrawal symptoms over a longer period of time</td>
<td>• 18 heavy marijuana users, age 31, 12 ex-users (age 37)</td>
<td>• open, non-randomized, controlled study</td>
<td>• increase in sleep difficulty until day 12 of abstinence, values elevated throughout abstinence, increase in strange dreams throughout abstinence</td>
</tr>
<tr>
<td>Haney, 2002</td>
<td>treatment of marijuana withdrawal symptoms</td>
<td>• 17 near-daily marijuana users (~half in placebo arm), age and gender not stated</td>
<td>• SB, cross-over, controlled study</td>
<td>• decrease in subjective ratings of sleep quality during withdrawal</td>
</tr>
<tr>
<td>Haney et al., 2004</td>
<td>oral THC or divalproex in the treatment of marijuana withdrawal symptoms</td>
<td>• 7 almost daily marijuana users in each study, mean age around 25</td>
<td>• DB, cross-over, controlled study</td>
<td>• THC study: no changes in objective measures, marijuana smoking increased “fell asleep easily” during withdrawal, increase in “strange dreams”</td>
</tr>
</tbody>
</table>

Table 39: Clinical studies assessing subjective sleep during marijuana withdrawal

The abstinence symptoms experienced by three adolescent heavy marijuana users are reported in the case study by Duffy and Milin (1996). Subjects sought treatment for cannabis-related problems. They were all initially interviewed by a child and adolescent psychiatrist and participated in psychiatric treatment programs. All of them met criteria for cannabis dependence. The first subject, male, 17 years of age, had a comorbid diagnosis of a conduct disorder and used alcohol occasionally. He experienced irritability, malaise, marijuana craving, agitation, sweating and initial insomnia within 24 to 48 hours of abrupt discontinuation of cannabis. These symptoms reached...
their peak after 3 to 4 days of abstinence, and normalized within 10 to 14 days. Insomnia and irritability were the last symptoms to abate.

The second patient was a 17-year-old female with a prior history of bulimia nervosa and infrequent use of cocaine and alcohol. She experienced similar withdrawal symptoms within 24 hours of abstinence. Her insomnia was successfully treated with 50 to 100 mg trazodone at bedtime. However, the patient relapsed after seven days, not tolerating the other withdrawal symptoms.

The third patient, male, 16 years of age, drank beer occasionally and had tried cocaine and LSD. Within 48 hours of discontinuation of marijuana use, he also experienced a similar set of withdrawal symptoms. These resolved within 10 days, with the exception of insomnia and irritability. Insomnia was then treated with 50 mg trazodone at bedtime for two weeks.

The case reports depict the time course of abstinence symptomatology in cannabis-dependent adolescents. However, the arbitrary selection and small number of subjects, the lack of a control group and the non-standardized collection of data constitute important limitations of the study.

Withdrawal symptoms after repeated controlled administration of oral THC doses were investigated by Haney et al. (1999a). Twelve daily marijuana users (mean age 24.7; 6 female) participated in a 20-day residential study. They were administered oral capsules containing Δ-9-THC or placebo at 10 A.M., 2 P.M., 6 P.M. and 10 P.M. in a single-blind manner. Bedtime was at 12 A.M. After a baseline period of three days on placebo, four doses of 20 mg Δ-9-THC each were given on the following four days. This was followed by an abstinence phase of four days on placebo. After four days with four doses of 30 mg Δ-9-THC, there was another withdrawal period of four days on placebo. In addition to a task battery of cognitive performance, vigilance and psychomotor ability, subjective effects were rated on visual analog scales and, in the mornings, the Saint Mary’s Hospital Sleep Questionnaire was completed.

Compared to baseline values, subjective ratings of “sedated” were increased significantly on day 1 of the 80 mg Δ-9-THC daily total condition, and decreased on days 2 and 3 of abstinence after 120 mg Δ-9-THC daily total. The subjective effect “trouble sleeping” was increased on day 1 of the 120 mg Δ-9-THC daily total condition and on day 4 of abstinence from 120 mg Δ-9-THC. The sleep questionnaire demonstrated that during abstinence from 80 mg Δ-9-THC daily, depth of sleep was significantly decreased on day 2, sleep quantity and sleep quality were decreased significantly on day 4. During abstinence from 120 mg Δ-9-THC daily, sleep problems were even slightly more pronounced.

The study was well-conducted. It is possible that baseline recordings were superposed by some abstinence effects from marijuana. However, in this case the sleep disturbances during withdrawal would in fact be of even greater magnitude.

A similar study for smoked marijuana was performed by the same investigators (Haney et al., 1999b). The twelve exclusively male participants of this study were almost-daily marijuana users with a mean age of 28 years. The study protocol was identical to the previous with a few exceptions: there were four instead of three days of baseline placebo. Instead of each oral 20 mg or 30 mg Δ-9-THC ingestion, subjects smoked five puffs of a marijuana cigarette containing either 1.8% Δ-9-THC or 3.1% Δ-9-THC. Tobacco cigarette smoking was controlled for, since puffs were counted and it was
determined whether amount of smoking differed across conditions. And finally, the order of low and high dosage Δ-9-THC phases was counter-balanced between individuals.

In contrast to the previous study, no significant changes in the sleep-related items of the visual analog scales or in the ratings of the Saint Mary’s Hospital Sleep Questionnaire were observed. Other measures changed in a similar way as in the other study: ratings of anxiety, irritability and stomach pain increased significantly during abstinence, and food intake decreased.

The study was well-conducted. It is not clear why subjective sleep measures did not achieve statistical significance in this comparable study. Superposition of initial withdrawal effects during baseline recordings might have played a role. However, this hypothesis would not be consistent with the observed differences in other measures. A more convincing explanation would be that due to the accelerated pharmacokinetics of marijuana smoking the earlier administrations (at 10 A.M., 2 and 6 P.M.) will not have influenced sleep as much as the earlier oral administrations in the other trial. It is also possible that sleep-modulating effects of other constituents of marijuana, in particular of CBD, which participants were not exposed to in the other trial, reduced the differences across conditions.

Budney et al. (2001) investigated withdrawal symptoms in twelve adult daily marijuana users (mean age 30.1; 5 female) in an outpatient setting. They were healthy, had no further dependence except for nicotine and had not used other illicit substances for 30 days. They were not seeking treatment for marijuana-related problems. After five days of baseline, during which participants were allowed to smoke as usual, subjects abstained from marijuana for three days. Then, the same protocol was repeated. Urine toxicology screens for marijuana and other illicit drugs confirmed compliance. Substance use diary, mood and craving questionnaires, the Marijuana Withdrawal Checklist and the Sleep Inventory were completed every day. The subjective assessments were confirmed by reports of “collateral observers” from the individuals’ environment who spent at least two hours with the participants every day.

Subjective ratings of sleep quality decreased significantly during both abstinence periods, as evidenced by the sleep questionnaire. This finding was confirmed by the Marijuana Withdrawal Checklist: the item “sleep difficulty” was significantly increased during both abstinence phases. It returned to baseline values during the second “smoking as usual” period. The item “strange dreams” increased significantly during the second abstinence phase. Further withdrawal symptoms observed in this study were craving for marijuana, decreased appetite and weight loss, but also aggression, anger, irritability and restlessness.

The study was well-conducted. The only apparent weakness is the lack of blinding with respect to drug condition.

Another outpatient study by Budney et al. (2003) examined the longer-term time course of marijuana withdrawal in 18 heavy marijuana users (mean age 30.9). They were not seeking treatment. During five baseline days, subjects were allowed to smoke as usual. This was followed by a period of 45 days of abstinence. Interactive voice responses were obtained through mandatory telephone calls at the same time each day. They assessed substance use, sleep and marijuana withdrawal symptoms. In addition to this, subjects visited the laboratory at least twice a week for additional mood and craving
questionnaires as well as breath alcohol assessments and urine toxicological screens for marijuana and other illicit drugs. Twelve ex-marijuana users (mean age 36.5) served as control subjects. Compared to mean baseline ratings, sleep difficulty was increased significantly until the 12th day of abstinence, and remained elevated throughout the 45-day assessment period. Starting on the second night of abstinence, the item “strange dreams” was increased significantly throughout the entire abstinence period. Effect sizes were in the medium to large range. Sleep difficulty and strange dreams were the two most common symptoms of clinical relevance. Other withdrawal symptoms were aggression, anger, anxiety, chills, craving, decreased appetite, decreased body weight, irritability, restlessness, stomach pain and sweating. In the control group, all measures remained unchanged across the trial. The investigators concluded that marijuana withdrawal is comparable with nicotine withdrawal with respect to the magnitude and time course.

The study results are impressive, in particular as to the importance of sleep disturbances. However, “having experienced withdrawal symptoms in the past” was an inclusion criterion. This arbitrary element may have resulted in a non-representative study sample, selecting participants who were more likely to experience abstinence effects during the trial.

Marijuana withdrawal symptoms after four days of controlled smoking and their treatment with the antidepressants bupropion and nefazodone were examined by Haney (2002). A separate experiment investigated the effectiveness of cannabis for treatment of weight loss in nine HIV-positive patients. However, sleep was not assessed in this trial.

Ten healthy, almost daily marijuana users (age and gender not stated) in the bupropion arm of the study spent 17 days in an inpatient facility after eleven outpatient days on placebo or bupropion. During the first four inpatient days, marijuana cigarettes containing 2.8% Δ-9-THC were smoked in five separate sessions throughout the day. This was followed by twelve days on placebo marijuana. Drug administration was single-blind. Afterwards, the same outpatient and inpatient protocol was repeated with an alternate dose of bupropion. Subjective sleep ratings were obtained every morning. The seven healthy subjects (age and gender not stated) in the nefazodone arm of the study were run on the same schedule with the exception that marijuana cigarettes contained 3.1% Δ-9-THC and that outpatient phases lasted only nine days.

It is assumed that about half of the altogether 17 participants in both study arms did not receive either antidepressant. In these, marijuana withdrawal was associated with decreased subjective ratings of sleep quantity. Withdrawal symptoms such as irritability, depression, decreased food intake, stomach pain, but also sleep quality were even worse in the bupropion-treated individuals, and they did not differ compared to placebo in the nefazodone subgroup. Both oral Δ-9-THC and smoked marijuana enhanced appetite in HIV-positive patients. Oral Δ-9-THC was more effective. However, subjective ratings for “drug liking” were higher for smoked marijuana.

No information about the volunteers is given. The article does not specify what was used as “placebo marijuana”. It is possible that it contained all active constituents other than Δ-9-THC. Furthermore, it is not clear by what method subjective sleep was assessed.
Similar, but more elaborate experiments were conducted by Haney et al. (2004) to test the effectiveness of oral Δ-9-THC and the mood stabilizer divalproex in the treatment of marijuana withdrawal symptoms. Divalproex is a stable coordination compound of sodium valproate and valproic acid in a 1:1 molar relationship. Seven almost daily marijuana users were recruited for each study. They were not seeking treatment. Mean age was 24 in the seven male subjects of the oral THC study, and 26 in the divalproex study (one female). Marijuana cigarettes contained either 3.0 or 0.0% Δ-9-THC and were smoked according to a standardized procedure. There were five smoking sessions per day, the last one at 10 P.M. After four baseline days during which active marijuana was given only in the last smoking session, there were four days of active marijuana smoking and then six days on placebo marijuana. According to a double-blind, cross-over design, participants were run twice on these 15-day inpatient phases, receiving either treatment with oral THC/divalproex or placebo. The inpatient periods were separated by an outpatient phase with no instructions about marijuana consumption. It lasted for five days in the oral THC arm and for two weeks in the divalproex study. Subjects in the THC arm were given placebo on all inpatient days except for one of the two withdrawal phases. They were administered five doses of 10 mg Δ-9-THC orally, each an hour before smoking sessions. Subjects in the divalproex arm started to take divalproex or placebo already 14 days prior to the experiment. Bedtime was from 12 A.M. until 8:15 A.M. The Nightcap sleep monitor was worn every night. However, equipment failed in three individuals. Their data were not included in the analyses. Tobacco smoking was controlled. Subjective effects, withdrawal symptoms, subjective sleep, memory, learning and psychomotor ability were assessed daily.

In the oral THC study, the Nightcap sleep monitor did not reveal any significant differences between conditions. The exact data are not given. During the active marijuana phase, subjective ratings of “fell asleep easily” were increased. During withdrawal, there was a tendency for an increase on the item “trouble sleeping” and a significant increase in “strange dreams”. Administration of oral THC decreased ratings of trouble sleeping. It also reduced craving, anxiety, chills, “feeling miserable” and it increased food intake. In the divalproex study, there were no effects of marijuana abstinence on any Nightcap sleep monitor measure nor on subjective ratings of sleep in the placebo condition. Divalproex increased TST during abstinence compared to placebo. However, subjective ratings of sleep were worse during abstinence: participants reported waking up earlier and waking up more often compared to placebo. Divalproex decreased craving, but it increased subjective ratings of anxiety, irritability, “feeling on edge”, sleepiness, yawning and “feeling withdrawn” and worsened performance on psychomotor tasks.

The study was well-conducted. As in the previous study, undetermined amounts of CBD in the placebo marijuana may have modulated sleep. It is not clear why the placebo group in the divalproex study did not experience sleep disturbances during marijuana withdrawal.

3.2.4.5. Effects of gestational cannabis exposure upon sleep

It was mentioned above (chapter 3.2.1.6.) that gestational exposure to cannabis is associated with increased θ spectral power and decreased α at birth, as well as increased arousals during active sleep and decreased β power at one year (Scher et al., 2000). There are two further studies which
investigated the sleep effects of prenatal exposure to cannabis (Scher et al., 1988; Dahl et al., 1995; see Table 40).

<table>
<thead>
<tr>
<th>Publication</th>
<th>Purpose of study</th>
<th>Subjects</th>
<th>Study design and data collection</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scher et al., 1988</td>
<td>effects of prenatal alcohol and marijuana on sleep at birth</td>
<td>55 exposed newborns, same number of controls</td>
<td>cohort study, mothers selected if 1 drink/d or 1 marijuana cigarette/d during 1st trimester, substance use interviews after each trimester, 2 h sleep recording at 24-36 h after birth, regression analyses</td>
<td>marijuana use during any trimester: increased small and large body movements, decrease in total quiet sleep and trace alternate quiet sleep, 1st trimester use also: decreased low voltage irregular active sleep, total active sleep unchanged, decrease in number of rapid eye movements</td>
</tr>
<tr>
<td>Dahl et al., 1995</td>
<td>effects of prenatal marijuana upon sleep at age 3 years</td>
<td>18 marijuana-exposed infants, age 3 years, 20 unexposed control children</td>
<td>cohort study, follow-up of a cohort, which also furnished data for Scher et al. (1988), follow-up assessments at 8, 18 and 36 months, PSG: 1 adaptation night, 2 consecutive nights of recording</td>
<td>exposure group with less SE, more WASO and more frequent arousals, positive correlation between small body movements at birth (Scher et al., 1988) and arousals at 3 years</td>
</tr>
<tr>
<td>Scher et al., 2000</td>
<td>effects of prenatal cocaine and other drug use on central nervous system development</td>
<td>37 cocaine-exposed neonates and 34 control infants, n=57 available for follow-up</td>
<td>cohort study, mothers selected if at least 1 line of powder cocaine/d or any crack during 1st trimester, PSG recordings for 120 min at 24-36 h postpartum and at 1 year</td>
<td>marijuana: increased θ energies and decreased α at birth, increased arousals during active sleep and decreased β energies at 1 year</td>
</tr>
</tbody>
</table>

Table 40: Studies investigating the sleep of infants born under the influence of cannabis

In the study by Scher et al. (1988), sleep at birth was examined in 55 newborns (mean gestational age 40.5 weeks) who were exposed to marijuana and/or alcohol during gestation. Newborns were selected out of 763 deliveries if the mother had consumed at least one drink or marijuana cigarette per day during the first trimester. The next infant born to a mother who reported a lesser amount of substance use served as a normal control. Substance histories were obtained in the fourth and seventh prenatal month and 24 hours after delivery. Two hours of sleep recordings were performed within 24 to 36 hours of birth and scored according to standard criteria (Anders et al., 1971). Regression analyses investigated the differential effects of exposure to alcohol, marijuana or nicotine during each trimester. The analyses also controlled for the use of other illicit drugs, for demographical data such as maternal age, educational level, income, race, marital status, for infant characteristics such as sex, birth weight, ponderal index and estimated gestational age, as well as for EEG technician.

Maternal marijuana use during each of the three trimesters predicted increased small and large body movements, decreased total quiet sleep and decreased trace alternate quiet sleep. First trimester exposure to marijuana additionally decreased low voltage irregular active sleep and decreased the number of rapid eye movements. Mixed active sleep was increased, so that the percentage of total active sleep remained unchanged. For illustration, subgroups were formed. The subgroup made up of neonates exposed to cannabis at least once a day during the first trimester had significantly less quiet sleep, more indeterminate sleep, more small and large body movements and a reduced REM density.
compared to the non-exposed subgroup. Alcohol consumption during the first trimester predicted increased indeterminate sleep and arousals, and tobacco exposure affected body movements only. The study was well-conducted. Overlapping acute or subacute withdrawal effects from cannabis exposure shortly before delivery were not controlled for.

As a follow-up of a larger cohort which also furnished the data for this previously analyzed study, Dahl et al. (1995) examined the sleep at the age of three years in 18 infants with gestational cannabis exposure. Mean daily exposure during the first trimester was 2.8 marijuana cigarettes. Twenty unexposed infants (less than 0.001 marijuana cigarettes per day) served as normal controls. The mothers of two groups did not differ in any demographical variables or with respect to household environment, attitudes towards the child and substance use history except for marijuana. After an adaptation night, children spent two more nights in the laboratory. Sleep stages were defined with the criteria by Rechtschaffen and Kales (1968).

The group of the exposed infants had a significantly lower SE, more WASO and more frequent arousals. Not achieving statistical significance, stage 2 sleep was reduced and REM sleep increased with a shorter REM sleep latency. The former would correspond to the decrease in quiet sleep found at birth. Comparison with the newborn data was difficult owing to the differences in sleep stage definitions between newborns and children. However, a significant, positive correlation was found between small body movements at birth (Scher et al., 1988) and arousals at three years of age. No obvious biases were detected in the critical analysis of the study.

3.2.4.6. Overview over sleep effects of cannabis
Animal experiments show an initial increase in wakefulness after administration of ∆9-THC, followed by an increase in SWS (see Table 41). REM sleep is suppressed. Repeated doses of marijuana lead to a reduction in SWS. In exchange, the drowsy state is increased. Upon withdrawal, a decrease in SWS and enhancement of the drowsy state can be observed. Sometimes, an REM rebound occurs.

It is difficult to generalize the findings from the available PSG studies of cannabis due to considerable heterogeneity with respect to the administered dosages, time and route of administration, specificity for ∆9-THC (or combination with CBD), previous drug consumption (leading to tolerance or withdrawal effects), individual expectations and emotional reactions to drug effects. Acute administration of ∆9-THC may decrease SOL. However, as an example for the heterogeneity between studies, an initial arousal is observed after the administration of a high dose to drug-naïve individuals. ∆9-THC increases stage 4 sleep, but reduces stage 3 sleep. REM sleep percentage and REM density are reduced. Sedative effects of ∆9-THC may still be present the next morning. Adding a low dose of CBD leads to a relative increase in wakefulness. Tolerance to SWS effects occurs after chronic administration of marijuana, whereas tolerance to REM sleep effects appears to be less pronounced. Upon cessation of cannabis consumption, SOL and WASO are increased and an REM rebound can be observed. Sleep disturbances constitute a frequently observed symptom of marijuana withdrawal.
Cross-sectional studies reveal that about two thirds of marijuana-dependent patients experience sleep problems during a cessation attempt. Sleep disturbances disappear with resumption of marijuana smoking, and apparently they can also be alleviated with low oral doses of Δ-9-THC.

At birth, infants with gestational exposure to cannabis present with increased body movements and less quiet sleep. At the age of three years, sleep continues to be disrupted, as evidenced by decreased SE and an increase in WASO and in arousals.

<table>
<thead>
<tr>
<th>Δ-9-THC</th>
<th>Acute administration</th>
<th>Chronic administration</th>
<th>Withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOL</td>
<td>▲;▼</td>
<td></td>
<td>▲</td>
</tr>
<tr>
<td>WASO</td>
<td>-</td>
<td></td>
<td>▲</td>
</tr>
<tr>
<td>TST</td>
<td></td>
<td>▼</td>
<td></td>
</tr>
<tr>
<td>Stage 1 %</td>
<td></td>
<td>▲</td>
<td>▲</td>
</tr>
<tr>
<td>Stage 2 %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 3 %</td>
<td></td>
<td>▼</td>
<td></td>
</tr>
<tr>
<td>Stage 4 %</td>
<td></td>
<td>▲</td>
<td></td>
</tr>
<tr>
<td>total SWS</td>
<td></td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>REM sleep %</td>
<td></td>
<td>▼</td>
<td>▲</td>
</tr>
<tr>
<td>REM latency</td>
<td></td>
<td>▲</td>
<td>▼</td>
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<tr>
<td>REM density</td>
<td></td>
<td>▼</td>
<td>▲</td>
</tr>
</tbody>
</table>

Table 41: Overview over the sleep effects of Δ-9-THC; ▲▼ arrows indicate findings from preclinical studies; ▲▼ arrows indicate studies in humans; boxes left in blank if data not sufficient or contradicting; - indicates no change

3.3. Effects of sleep disturbances upon vulnerability to substance use

3.3.1. Study characteristics

Ten studies were eligible for analysis. Out of these, there were four cross-sectional studies and six cohort studies (see Table 42). Most studies do not differentiate between substance classes.

<table>
<thead>
<tr>
<th>Vulnerability to drug use</th>
<th>Case report</th>
<th>Cross-sectional study</th>
<th>Cohort study</th>
<th>Case-control study</th>
<th>Clinical study</th>
<th>Sum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>4</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>10</td>
</tr>
</tbody>
</table>

Table 42: Classification of studies examining the effects of sleep disturbances upon the vulnerability to substance use
3.3.2. Impact of sleep disturbances upon vulnerability to subsequent onset of drug abuse

There are four cross-sectional studies that provide information upon the association between sleep disturbances and substance use (see Table 43). They are not capable of establishing a temporal or causal relationship. It is not clear to what extent sleep effects of drug use are described, to what extent effects of preexisting sleep problems upon subsequent drug use and to what extent effects of independent mediators of the observed association. Furthermore, the surveys depend on the accuracy of the participants' reports on drug use. Since sleep problems are scored with dichotomous variables in these studies, the differential effects of sleep problems of greater or smaller severity are not accounted for.

<table>
<thead>
<tr>
<th>Publication</th>
<th>Purpose of study</th>
<th>Subjects</th>
<th>Study design and data collection</th>
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<tbody>
<tr>
<td>Webb et al., 1996</td>
<td>prevalence of alcohol and drug use in UK</td>
<td>• 3075 UK university students</td>
<td>• survey</td>
<td>• 5% of students experience with cocaine, 18% LSD, 13% ecstasy, 57% cannabis</td>
</tr>
<tr>
<td></td>
<td>university students</td>
<td>• age 21</td>
<td>• substance use questionnaire including other lifestyle variables such as sleep quality, anxiety/depression</td>
<td>• 69% of students sleep difficulties</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 47% female</td>
<td></td>
<td>• no relationship between sleep problems and alcohol or drug use</td>
</tr>
<tr>
<td>Vignau et al., 1997</td>
<td>prevalence of sleep problems among French secondary school students</td>
<td>• 763 French secondary school students</td>
<td>• survey</td>
<td>• 41% sleep problems</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• mean age 17</td>
<td>• questionnaire of sleep complaints, but also of personal and family disorders</td>
<td>• 7% of students illicit drug experience</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 40% female</td>
<td></td>
<td>• positive correlation between sleep complaints and illicit drug experience</td>
</tr>
<tr>
<td>Johnson and Breslau, 2001</td>
<td>association between sleep disturbance and substance use in adolescence</td>
<td>• 13831 adolescents</td>
<td>• survey</td>
<td>• use of any illicit drugs associated with more sleep problems compared to non-users</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ages 12-17</td>
<td>• data from National Household Survey on Drug Abuse</td>
<td>• when adjusting for externalizing and internalizing problems, results remained significant for use of illicit drugs (alone or in combination)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 51% male</td>
<td>• checklist of psychiatric problems (including ‘trouble sleeping’) within past 6 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• substance use within past year</td>
<td></td>
</tr>
<tr>
<td>Beaujouan et al., 2005</td>
<td>prevalence of substance use disorders among French anaesthetists and related work conditions</td>
<td>• 3357 French anaesthetists</td>
<td>• survey</td>
<td>• 0.7% cannabis abuse, 0.2% stimulant abuse</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 36% female</td>
<td>• questionnaire administered to all French anaesthetists, containing 93 items, covering drug consumption and associated work conditions</td>
<td>• anaesthetists with abuse of any substance (including nicotine and alcohol) with more frequent complaints of sleep deprivation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• correlation NS for illicit drugs only</td>
</tr>
</tbody>
</table>

Table 43: Cross-sectional studies that examined the association between sleep disturbances and drug use

A survey by Webb et al. (1996) investigated the prevalence of substance use in United Kingdom university students. Sleep problems were only a secondary outcome measure. A questionnaire was personally administered to 3075 randomly chosen second-year students (mean age 20.9; 47% female) from universities of the United Kingdom. The questionnaire was filled out during scheduled lecture hours. It gathered information upon demographic variables, substance use, sleep quality and anxiety/depression ratings. It was completed by practically all students. Correlations between variables were calculated using Chi-square tests.

11% of students did not drink. 61% of male drinkers and 48% of female drinkers exceeded “sensible” weekly levels of drinking. 5.4% of students had experience with cocaine or crack, 17.6% with LSD, 12.9% with ecstasy and 57.1% with cannabis, respectively. 69% of all participants reported some kind
of sleep difficulties. However, there was no significant association between sleep problems and alcohol or drug use. Anxiety/depression of relevant severity was frequently reported, however not related to substance use either.

The presence of sleep problems was evaluated by “yes or no” questions, that is in a manner which registered also problems of lighter severity. Furthermore, it can be assumed that not only regular drug users, but all students who had any experience with illicit drugs formed the group of “drug users”. These broad definitions might have impeded the detection of significant correlations.

Vignau et al. (1997) examined the prevalence of sleep problems and their correlates among 753 French secondary school students. The students were chosen randomly. 40% were female, and mean age was 17 years. The self-report questionnaire included five main items of sleep quality assessment. These were bad sleep quality, trouble falling asleep, occurrence of early awakenings, sleeping pill intake and need for daytime sleep. These parameters yielded a composite variable of either good or poor sleep. The questionnaire also investigated substance use histories, antisocial behavior, suicide, the presence of a somatic illness and weight problems as well as the parents’ marital status, their health and psychiatric problems.

41% of the students reported some type of sleep complaints, 7% reported experience with illicit drugs. There was a significant correlation (P<0.001) between these two items. However, this association remained significant only for the subgroup of boys and not for girls. Poor sleep was associated with a great number of further personal or family troubles, such as chronic somatic disease, use of psychoactive medication, weight problems, cigarette smoking, inebriation experience, theft and truancy, suicidal ideas and suicide attempts, divorce of the parents, parental anxiety, psychoactive treatment or chronic somatic illness. Also, girls had more sleep complaints than boys, and there were differences for type of high school and the students’ living place.

Prior use of illicit drugs was surprisingly infrequent in this sample (only 7% of students compared to about 50% in U.S. American 10th or 12th graders in the 1997 Monitoring the Future survey (National Institute on Drug Abuse, 2006). This suggests a confounding element, that the students in this study may have had some doubts about the confidentiality of their responses.

The study by Johnson and Breslau (2001) used preexisting data from the National Household Survey on Drug Abuse. The sample of this survey comprised 13831 adolescents (ages 12 to 17; 49% female) from the general U.S. American population. The survey employed the Youth Self-Report checklist to examine the presence of somatic complaints, anxiety and depression within the past six months, for a composite scale of internalizing problems, and of delinquent or aggressive behavior as externalizing problems. Items of the checklist were marked as either “not true”, “sometimes true” or “often true”. The checklist also contained the item “trouble sleeping”. Sleep problems were defined as “trouble sleeping often in the past six months”. Subjects who reported “not having trouble sleeping” or “sometimes having trouble sleeping” were considered as good sleepers. Furthermore, use of tobacco, alcohol and any illicit drugs during the past year was ascertained. Trouble sleeping was significantly more frequent among users of illicit drugs compared to non-users, even when adjusted for demographics. When internalizing and externalizing scale scores were treated
as covariates, results remained significant for use of illicit drugs only, use of illicit drugs and alcohol, and for use of illicit drugs, cigarettes and alcohol. In contrast to this, the differences in the frequency of sleep problems were no longer significant for use of cigarettes only, alcohol only, as well as alcohol and cigarettes without illicit drugs. There appeared to be a positive correlation between the frequency of substance use and sleep problems, however this relationship was not consistent. The associations between sleep problems and illicit drug use were stronger for female participants than for male. However, these differences disappeared after correcting for internalizing and externalizing problems. The study was conducted well.

A survey of the prevalence of substance abuse among French anaesthetists and associated work conditions was carried out by Beaujouan et al. (2005). Sleep disturbances were not a primary outcome measure. A questionnaire covering drug consumption within the past twelve months was administered to all 9186 French anaesthetists. Demographical data and information upon work conditions, among them a perceived sleep deprivation, were also obtained. A total of 3476 questionnaires were returned. 36% were female, and the majority (78%) were between 36 and 55 years of age. 3357 of the anaesthetists furnished information about substance use, and 2744 (30% of all anaesthetists) completed all items so that they could be included in the statistical analyses of independent risk factors.

0.7% of respondents (i.e. n=23) admitted abuse of or dependence on cannabis, 0.2% (i.e. n=7) reported abuse of or dependence on stimulants, i.e. amphetamines or cocaine. The prevalence of abuse or dependence on tobacco, alcohol and sedative-hypnotics was 8.9%, 6.5% and 4.5% respectively. Individuals with abuse of any substance, including alcohol, nicotine and hypnotics, had significantly more frequent complaints of sleep deprivation as a working condition. However, the perceived sleep deprivation was an independent risk factor only for abuse of nicotine and of sedative-hypnotics. Abuse of opiates, cannabis and stimulants was correlated positively with consumption of tobacco and of sedative-hypnotics, however not significantly with the perception of sleep deprivation. The lack of a statistically significant correlation might be due to the relatively small number of anaesthetists who admitted abuse or dependence on cannabis or stimulants (less than 1%). Furthermore, only 30% of the anaesthetists who received the questionnaire responded to all of its items. This low response rate may have resulted in non-representative sample. The definition of “sleep deprivation” as a working condition is different from definitions of sleep difficulties in other studies.

There are four longitudinal studies which examined the incidence of substance use among persons with sleep problems compared to good sleepers (see Table 44).
Table 44: Prospective studies assessing the association between sleep disturbances and onset of drug use

<table>
<thead>
<tr>
<th>Publication</th>
<th>Purpose of study</th>
<th>Subjects</th>
<th>Study design and data collection</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ford and Kamerow, 1989</td>
<td>association</td>
<td>• 7954 at follow-up&lt;br&gt;• 60% female&lt;br&gt;• age 18 and over</td>
<td>• survey and cohort study&lt;br&gt;• data from Epidemiologic Catchment Area Study (1981-85)&lt;br&gt;• 2 interviews separated by 1 year&lt;br&gt;• information upon psychiatric disorders and sleep disturbances collected with the Diagnostic Interview Schedule</td>
<td>• prevalence of drug abuse higher among individuals with insomnia&lt;br&gt;• insomnia at second interview (or at both) associated with new onset of depression, but also anxiety and alcohol abuse, presumably NS for drug abuse</td>
</tr>
<tr>
<td>Weissman et al., 1997</td>
<td>association</td>
<td>• about 5550 at follow-up&lt;br&gt;• mean age 48.1</td>
<td>• survey and cohort study&lt;br&gt;• analyses from the same Epidemiologic Catchment Area Study data&lt;br&gt;• only considering subjects who had insomnia in past year and those with neither insomnia nor psychiatric disorder</td>
<td>• 8% of people with insomnia and a psychiatric disorder in past year had drug abuse&lt;br&gt;• persons with insomnia and no psychiatric disorder had odds ratio of 1.9 for onset of drug abuse within following year (NS)</td>
</tr>
<tr>
<td>Breslau et al., 1996</td>
<td>association</td>
<td>• 979 at follow-up&lt;br&gt;• ages 21-30</td>
<td>• survey and cohort study&lt;br&gt;• 2 interviews separated by 3.5 years&lt;br&gt;• information upon psychiatric disorders and sleep disturbances collected with the Diagnostic Interview Schedule</td>
<td>• prevalence of drug abuse higher among individuals with sleep disturbances&lt;br&gt;• incidence of drug abuse higher in subjects with prior history of sleep disturbance compared to those with no sleep disturbance&lt;br&gt;• OR even higher for hypersomnia</td>
</tr>
<tr>
<td>Wong et al., 2004</td>
<td>association</td>
<td>• 258 Caucasian boys&lt;br&gt;• 60% from alcoholic families, 40% controls</td>
<td>• cohort study&lt;br&gt;• mothers’ ratings of child’s sleep problems at age 3-5 and of attention problems, anxiety/depression and aggression at age 9-11&lt;br&gt;• at age 12-14, adolescents provided substance use histories</td>
<td>• early onset of both marijuana use alone and use of any illicit drugs (also of alcohol and nicotine) correlated positively with overall sleep problems at age 3-5, as well as with &quot;being overtired at 3-5&quot;, but not with &quot;having trouble sleeping at 3-5&quot;&lt;br&gt;• correlation not mediated by factors assessed at age 9-11</td>
</tr>
</tbody>
</table>

Ford and Kamerow (1989) analyzed data from the National Institute of Mental Health Epidemiologic Catchment Area Study between 1981 and 1985 to examine the prevalence of sleep disturbances in the general population, their relationship to simultaneous psychiatric disorders and the incidence of new cases of psychiatric disorders. Out of the initial 10534 adult participants, 7954 (76%) were available for both baseline and follow-up interview one year later. 60% of these were female, and the majority (62%) were between 26 and 64 years old. At baseline and follow-up, both face-to-face interviews, sleep problems and psychiatric symptoms were assessed with the National Institute of Mental Health’s Diagnostic Interview Schedule. This instrument is a highly structured interview that is administered by trained lay persons. The criteria for sleep problems are based on the persistence of symptoms for two weeks, in contrast to the four weeks required for DSM-IV diagnosis of a sleep disorder.

At the baseline interview, 10.2% of the participants reported insomnia and 3.2% hypersomnia. Among these individuals, psychiatric disorders were significantly more prevalent compared with those who reported no sleep problems. The relationship was strongest for anxiety disorders, but was also significant for depressive disorders, alcohol abuse and drug abuse. Those individuals whose insomnia had not resolved by the follow-up interview were at a greater risk of new onset of depression, but also of anxiety disorders and alcohol abuse. Insomnia first reported at follow-up was also associated...
significantly with new onset of these psychiatric disorders. Hypersomnia at any of the two interviews was related to a higher incidence of depression and anxiety disorders. Since drug abuse is not mentioned in this section of the article, it is presumed that no significant relationship was found.

The same data from the Epidemiologic Catchment Area Study were analyzed by Weissman et al. (1997) in order to examine the incidence of psychiatric disorders among persons with insomnia. Out of the 10534 individuals at the baseline interview, only 7113 were relevant for the study. Only the following three groups of persons were taken into consideration: subjects who had never had insomnia or a psychiatric disorder, those who had insomnia in the past year, but never a psychiatric disorder, and those who had both insomnia and a psychiatric disorder in the past year. Their mean age was 48.1 years. 78% were available for the follow-up interview one year later.

Out of the individuals who had insomnia and a psychiatric disorder in the year before the follow-up interview, 8% were drug abusers. Subjects with a history of insomnia, but no other psychiatric disorder within the past year had a significantly greater risk for first onset of depression, panic disorder or alcohol abuse during the following year compared to individuals with no history of insomnia or a psychiatric disorder. In subjects with insomnia and no psychiatric disorder, the odds ratio for first onset of drug abuse during the following year was 1.9. However, this finding was not statistically significant.

One needs to hold in mind that the two cited studies analyzed the same data in similar ways. Hence, the studies’ findings must not be interpreted as independent confirmations of one another. Follow-up was slightly below 80%. Hence, there may be some selection bias. The Diagnostic Interview Schedule may underdiagnose drug abuse disorders, according to the principle of social desirability and since individuals might be reluctant to report illegal activity to lay interviewers from an institute funded by the U.S. Government. The participants’ mean age was fairly old for the analyses of drug abuse. Subjects with no previous drug abuse and a mean age of 48 are very unlikely to develop a drug abuse disorder in the subsequent year. This might have impeded significant results. Also, the time span between the two assessment points was only one year. A significant relationship for drug abuse might have been apparent after a longer interval.

The association between sleep disturbance and psychiatric disorders was examined both cross-sectionally and prospectively by Breslau et al. (1996). Out of an initial random sample of 1200, 1007 young members of a health maintenance organization (ages 21 to 30) were interviewed based on the Diagnostic Interview Schedule to gather information upon lifetime psychiatric disorders. Depressive symptoms and the occurrence of insomnia and hypersomnia were investigated specifically in all participants. 979 subjects were reinterviewed 3.5 years later, when the interval history of new onset of psychiatric disorders was obtained.

Lifetime prevalence of insomnia alone was 16.6%, of hypersomnia alone 8.8%, and of combined insomnia and hypersomnia 8%. Among, individuals with a history of sleep disturbance, the prevalence of major depression, anxiety disorders, alcohol, nicotine and illicit drug abuse or dependence was significantly higher than among persons without a history of sleep disturbance. The follow-up interviews revealed that the incidence of major depression, any anxiety disorder, nicotine dependence, and particularly drug abuse or dependence was significantly higher among individuals with a history of
prior insomnia. The gender-adjusted odds ratio for the onset of drug abuse or dependence among insomniacs was 7.2, with a confidence interval of 2.1 to 24.2. Among individuals with a history of hypersomnia, the risk of new onset of major depression, alcohol, nicotine or illicit drug abuse or dependence was significantly increased as well. Compared to subjects without a history of prior hypersomnia, the gender-adjusted odds ratio for drug abuse or dependence was as high as 13.4 with a confidence interval of 4.0 to 45.4.

The study only adjusted for gender, and not for potential covariates such as age, educational level, socioeconomic status and psychiatric disorders such as attention deficit/hyperactivity disorder (ADHD). It cannot be ruled out that the impressive odds ratios found in this study may be accounted for by the investigators’ failure to adjust for these variables.

A prospective study on the relationship between sleep problems early in life and subsequent onset of alcohol and drug use was carried out by Wong et al. (2004). At ages 3 to 5, 311 Caucasian boys from alcoholic fathers and a non-specified number of age-matched boys from control families were assessed with semi-structured interviews and interactive tasks. In addition to the assessment of parental alcoholism, these interviews at age 3 to 5 included mothers’ ratings of two items regarding the child’s sleep, “overtiredness” and “having trouble sleeping”. The answers were given numerical values, 0 for “not true”, 1 for “sometimes true” and 2 for “often true”. Since few boys were assigned the highest score of two, dichotomous variables were formed ex post, with 0 denoting “not true” and 1 “sometimes or often true”. The two items were also collapsed to form a composite indicator of overall sleep problems. This means that in contrast to other studies, boys who “sometimes had sleep problems” were considered “poor sleepers”. In late childhood, at age 9 to 11, the boys were rated again by their mothers, this time with respect to attention problems, anxiety, depression and aggression. At ages 12 to 14, boys completed the Drinking and Other Drug Use History Questionnaire, which provided information upon drinking, drunkenness, cigarette smoking, marijuana and other illicit drug use. Only those boys who actually provided substance use history at this age were included in the analyses. The final sample consisted of 258 boys, 60% from alcoholic fathers and 40% from control families.

Use of alcohol, cigarettes, but also of marijuana alone and use of any illicit drugs at ages 12 to 14 was correlated positively and significantly with the composite indicator of overall sleep problems at age 3 to 5. Moreover, this early onset of substance use was significantly correlated with the single item “overtiredness” at age 3 to 5, but not with “trouble sleeping”. Sleep problems at age 3 to 5 also predicted attention problems and anxiety/depression at ages 9 to 11. However, a statistical analysis which first held constant the effects of sleep problems and then the effects of these potential mediators demonstrated that neither attention deficits nor anxiety/depression (nor aggression) mediated the effects of sleep problems upon early onset of substance use.

The study contains a few limitations. The study sample may not be representative. Only Caucasian boys were studied, and the majority came from high-risk families. There may be some selection bias since only those subjects who provided information on substance use were accounted for in the analyses. The ex-post changes in the numerical codings constitute a methodological bias. In addition to the aforementioned dichotomous rating scale of sleep problems, behavioral problems were ex post regarded as continuous variables. Furthermore, the evaluation of sleeping problems by the mothers
and only with respect to the items “overtiredness” and “having trouble sleeping” is not equivalent to a psychiatric diagnosis. On the other hand, the early onset of substance use is not necessarily associated with subsequent drug abuse or dependence.

### 3.3.3. Predictive value of sleep disturbances for relapse

There has been only insufficient research on the question whether sleep abnormalities constitute a risk factor for relapse in abstinent drug users. There are two prospective studies which investigated whether drug dreams predict treatment outcome in abstinent drug users (see Table 45).

<table>
<thead>
<tr>
<th>Publication</th>
<th>Purpose of study</th>
<th>Subjects</th>
<th>Study design and data collection</th>
<th>Results</th>
</tr>
</thead>
</table>
| Christo and Franey, 1996     | dreams during withdrawal from illicit drugs and predictive value for outcome | • 101 drug users from London  
• 26% female  
• 80% between 20 and 34 years | • prospective cohort study  
• baseline interview at 6 wk abstinent  
• interim meeting after 7 wk  
• follow-up 6 months after baseline interview  
• dreams and related events assessed at these interviews | • drug dreams reported more frequently during initial abstinence  
• decrease in frequency of drug dreams with continued abstinence  
• dream frequency at baseline positively correlated with relapse at follow-up; relationship most prominent for cocaine  
• drug dreams correlated positively with drug craving and with sleep disturbance |
| Reid and Simeon, 2001        | dreams during withdrawal from crack and predictive value for outcome | • 46 male crack users from Trinidad and Tobago  
• 80% between 20 and 39 years | • prospective cohort study  
• 3-month inpatient phase  
• first month of inpatient phase and 6 months after discharge, daily dream questionnaires including contents and feelings | • during 1st month of abstinence, frequent drug dreams, feelings of urges during the dream and relief upon awakening  
• at 6 months follow-up, drug dreams less frequent, less feelings during the dream and upon awakening  
• awakening with urges after drug dreams positively correlated (NS) with relapse |

Table 45: Prospective studies investigating the predictive value of dream characteristics for treatment outcome in abstinent cocaine users

Christo and Franey (1996) examined drug dream frequency and emotional responses in 101 abstinent users of illicit drugs in London. 26% of participants were female, and the majority (80%) were between 20 and 34 years of age. They were seeking treatment for drug-related problems, and at the time of the baseline interview had been abstinent for six weeks from their drug of choice. A drug-related dream questionnaire investigated the occurrence and frequency of drug dreams when using the drug and since abstinence, but also emotional responses to these dreams. After another seven weeks, there was an interim meeting. In addition to the dream questionnaire, participants were asked whether they had lapsed in the meantime. Also, an event questionnaire was completed which examined the presence of factors that might have contributed to lapse. It contained 31 items such as negative affect, drug-related cues and social pressure. About 90% of the patients were available for the comprehensive follow-up interview about six months (mean of 204 days) after baseline.

The occurrence of drug dreams was reported by significantly more patients during initial abstinence compared to when they last used drugs. The occurrence of drug dreams decreased with continued abstinence. The frequency of drug dreams at baseline was significantly and positively correlated with drug use at follow-up. This relationship was most pronounced for cocaine. The emotional responses to these dreams, which were often slightly unpleasant feelings, slightly guilt provoking and quite
upsetting, were not correlated with treatment outcome. Furthermore, drug dreams at follow-up were significantly associated with drug craving and sleep disturbances at follow-up. In 26% of all lapse accounts, drug dreams were cited as a contributing factor, in addition to sensation seeking, negative mood and drug availability.

Limitations of this study are the polydrug usage of participants and the circumstance that recent drug consumption corresponded to the usual substance use patterns in only one third of patients. The others had needed to adapt their drug use to the restrictions in a prison or institution. Furthermore, data upon drug dreams were only collected at the three interviews. Daily dream diaries would have minimized recall bias.

Reid and Simeon (2001) examined dream contents in 57 male, treatment-seeking crack cocaine abusers during abstinence. The study was carried out in Trinidad and Tobago. 46 (81%) of the participants were available for follow-up. 80% of this final sample were between 20 and 39 years old. 96% of participants were polydrug users, and the treatment plan stipulated abstinence from all agents. During the first month of a three-month inpatient program, subjects filled out dream questionnaires and described the dream contents in relation to crack cocaine and their emotional responses to these dreams. Patients attended weekly outpatient sessions after the residential phase. During the sixth month after discharge, dream questionnaires were completed again.

In the first month of abstinence, frequent drug dreams were reported, mainly of smoking crack. Patients felt pleasures and urges of using the drug during the dream and felt relief upon awakening. At the follow-up six months after the inpatient phase, drug dreams were less frequent. Half of those subjects who dreamt of using the drug did not report any feeling upon awakening. Others dreamt of refusing the drug, which was not accompanied by feelings during the dream and either relief or no feeling upon awakening. Abstinence at six months was not correlated significantly with any dream contents or associated feelings in the first month. Having dreams of crack cocaine at six months follow-up and having dreams of refusing the drug were significantly associated with abstinence at six months follow-up. However, apparently, dreams of refusing the drug were only reported at six months follow-up. Furthermore, the investigators mention a logistic regression analysis which showed that having crack cocaine dreams at six months follow-up was a “predictor” of abstinence at six months follow-up. An interesting, albeit non-significant observation is mentioned somewhat casually in the discussion section of the article. Patients who awakened with urges after drug dreams during the first month of abstinence had a tendency to relapse more often by six months follow-up.

At first glance, this study’s “main” finding appears to contradict that reported by Christo and Franey (1996), because drug dreams were correlated positively with relapse in the earlier study and with continued abstinence in this one. However, the investigators’ affirmation that drug dreams predict continued abstinence is questionable. There were only associations between dreams at six months follow-up and abstinence at six months follow-up. This simultaneous coexistence is simply related to the circumstance that drug dreams abate with the resumption of drug abuse. The same observation was also made in the aforementioned study. Limitations of the present study are the lack of female participants, the polydrug usage in 96% of the subjects and possible interindividual differences in self-perception that may have confounded the observations of dream frequency and characteristics.
4. Discussion

4.1. Principal findings and their implications

4.1.1. Impact of illicit recreational drugs upon sleep

It has been clearly shown that illicit recreational drugs cause clinically relevant disturbances of sleep. In primary care settings, health professionals need to consider the possibility that drug abuse may be responsible for or contribute to complaints of sleep problems, especially among adolescents and young adults. The extreme form of such a contribution would be a sleep disorder secondary to substance use. According to DSM-IV criteria (American Psychiatric Association, 1994), this diagnosis can be made if the sleep disturbance is sufficiently severe to cause significant distress or impairment and to merit independent clinical attention, and if, on the other hand, a convincing temporal and causal relationship can be established to substance use or withdrawal. In these cases, failure to consider this differential diagnosis not only impedes adequate treatment of the sleep disturbance. But in addition to that, the opportunity of an early recognition and treatment of a substance use disorder is also missed.

4.1.1.1. Cocaine

The stimulant effects of cocaine have been demonstrated. After acute administration, wakefulness is increased and REM sleep is suppressed. These effects are similar to those elicited by other psychostimulants such as amphetamine (Feinberg et al., 1974).

During acute cocaine withdrawal, individuals generally experience pronounced difficulty sleeping. It has been shown that total sleep time is extremely short in abstinent cocaine abusers. During the first nine days of withdrawal, patients sleep only for a pooled mean of 366 minutes per night. In a recent study, the mean TST before treatment in 62 chronic insomniacs was a similar 359 minutes (Jacobs et al., 2004). Furthermore, mean sleep onset latency is 25 minutes during acute cocaine withdrawal, and the pooled sleep efficiency is 86%. Cocaine has a half-life of about one hour, its metabolites are not active and cocaine effects disappear within three hours of nasal application (see chapter 1.2.1.3.). Therefore, the observed sleep disturbance cannot be explained by residual cocaine effects.

The REM rebound during acute cocaine withdrawal is consistent with the REM suppressing properties of cocaine. The meta-analysis showed a mean REM sleep latency of only 59 minutes in abstinent cocaine-dependent subjects. A meta-analysis of PSG studies in patients suffering from depression yielded a mean REM sleep latency of 58 minutes (Hudson et al., 1992). Although depressed mood is a frequent symptom of cocaine withdrawal, the short REM sleep latency cannot be attributed to depression in the analyzed studies. Participants had low ratings of depressed mood, with exception of the first two withdrawal days in the study by Kowatch et al. (1992).

The pooled mean values for total sleep time during subacute abstinence yielded only 344 minutes in the meta-analyses, which is significantly lower than the values during acute withdrawal. This value is also lower than the TST in untreated chronic insomniacs (Jacobs et al., 2004). Furthermore, the
pooled mean SOL yielded 33 minutes and SE 82%. These findings are the exact opposite of what would be expected. The sleep disturbance does not abate with continued abstinence, but it even worsens after 10 days of abstinence.

The increments in REM sleep do not disappear during subacute withdrawal, even in the absence of depressed mood. The pooled mean value for REM sleep latency yielded only 55 minutes.

What makes these findings even more outstanding is the circumstance that subjective sleep measures improve or at least remain unchanged in all of the studies of cocaine withdrawal conducted to date. During subacute withdrawal, patients do not report any, or only very mild, sleep problems.

This phenomenon is unique in sleep medicine. It is the exact opposite of the well-known phenomenon of distorted sleep perception in primary insomniacs. After a night in the sleep laboratory, primary insomniacs may report serious sleep difficulty, or even assure that they did not fall asleep at all, although polysomnography reveals normal or only slightly disturbed sleep. For instance, insomniacs typically overestimate their sleep onset latency (Coates et al., 1982), whereas cocaine-dependent subjects underestimate their sleep onset latency during subacute withdrawal (Pace-Schott et al., 2005a; Morgan et al., 2006).

Research is still needed to investigate why sleep perception is distorted in this way during subacute cocaine withdrawal. It has been shown (Morgan et al., 2006) that arousals are reduced during this phase which may convey the impression of a greater sleep quality. Moreover, an increased proportion of δ spectral power is associated with better self-reports of sleep quality (Krystal et al., 2002). Although SWS as a percentage of TST is low both during acute and subacute cocaine withdrawal (see chapter 3.2.1.4.), δ spectral power may increase during subacute withdrawal (Morgan et al., 2006).

The current meta-analysis furnished clear evidence of considerable decrements in total sleep time. However, this does not prove that the lack of sleep is pathologic, or that the lack of sleep has any clinical relevance.

In two well-conducted studies which considered cognitive performance during cocaine withdrawal (Pace-Schott et al., 2005b; Morgan et al., 2006), reaction time on vigilance tasks as well as immediate and delayed verbal recognition deteriorated with continued abstinence. As demonstrated by Graw et al. (2004), differences in reaction times on the psychomotor vigilance task are a sensitive measure of growing sleep pressure in the context of sleep deprivation. On the other hand, motor skills have been shown to improve over a night of sleep (Walker et al., 2002). These improvements do not occur over an equivalent period of waking. The study by Morgan et al. (2006) demonstrated that in cocaine-dependent subjects, overnight improvements on a motor sequence task correlated positively with an individual’s total sleep time. This sleep-dependent procedural learning worsened across abstinence. Thus, the decreases in TST do not appear to be a function of more restorative sleep or of a reduced need for sleep during subacute withdrawal from cocaine. It is likely that the decrements in TST are pathologic.

Studies of the cognitive effects of sleep deprivation indicate that the sleep disturbances observed in abstinent cocaine users may very well be of clinical importance. Sleep deprivation of great magnitude may be associated not only with impairments of learning, both procedural and declarative (Walker and
Stickgold, 2004), but also with a deterioration of frontal executive functioning, as evidenced by Killgore et al. (2006). In this study, decision making under uncertainty was impaired after 49 hours of sleep deprivation in healthy subjects. Participants showed more risk-taking behavior after sleep deprivation. In another study (Killgore et al., 2007), moral judgment was compromised after two nights of sleep deprivation. The participants had greater difficulty to take decisions on emotionally evocative dilemmas and were more willing to violate personal moral beliefs.

The demonstrated impairments of vigilance and learning performance may put cocaine users at increased risk of relapse. Parenthetically, it is noteworthy that the subacute phase of cocaine withdrawal, when sleep and cognitive functioning are most compromised, is simultaneous to phase 2 of Gawin and Kleber's model (1986), when individuals are at the greatest risk of relapse.

There is need for randomized controlled trials in which cocaine-dependent subjects are assigned to receive either a placebo or a medication for sleep disturbance during cocaine withdrawal. These two groups will need to be compared with respect to treatment outcome. Studies of this kind are necessary in order to confirm the hypothesis that the observed sleep disruption has clinical relevance. A similar approach to combat sleep disturbance in alcoholics has proven to be associated with better treatment outcome (Monnelly et al., 2004).

It is not clear what substance would be adequate in this particular situation. Hypnotics with a high abuse potential such as benzodiazepines do not appear to be an option. It is an intriguing fact that among the most promising candidates as medications for cocaine dependence, there are three substances with gamma-aminobutyric acid (GABA)-mediated sedative properties. These drugs are tiagabine, a selective reuptake inhibitor of gamma-aminobutyric acid (GABA), topiramate, an anti-epileptic with agonist activity at GABA-A receptors (Sofuoglu and Kosten, 2006), and also baclofen, an agonist at GABA-B receptors (Roberts, 2005; Haney et al., 2006).

The diametrically opposed, but equally promising approach to promote better treatment outcome in abstinent cocaine users would be to administer a stimulant substance. Such a medication would treat the detrimental effects of the sleep deprivation. For instance, modafinil has been demonstrated to restore cognitive functioning in sleep-deprived individuals (Wesensten, 2006). Therefore, it is very remarkable that modafinil has also been suggested to be effective in cocaine abuse (Dackis et al., 2005; Hart et al., 2007). The question of whether modafinil possesses abuse potential has been discussed controversially (Kruszewski, 2006; O'Brien et al., 2006).

Depending on demographic characteristics of the study sample such as race and on the method of determining drug use, estimates of the prevalence of cocaine use in pregnant women vary substantially. In a self-report survey of 2613 women, sponsored by the National Institute on Drug Abuse (1995), 1.1% admitted cocaine use during pregnancy. Reviewing five earlier studies on gestational cocaine use, Bendersky and Lewis (1999) estimated that at least 8% of children born in the U.S. were exposed to cocaine during pregnancy. A recent study with a sample of almost 12000 neonates found a total exposure rate of 9.1% (Bauer et al., 2005). It corrected the mothers’ self-reports by means of meconium screens, but it considered a high percentage of African-American mothers (49%).
Preclinical studies have suggested important interactions between prenatal cocaine effects and the circadian clock. After cocaine administration to pregnant hamsters, the circadian timing system in exposed litters was significantly altered (Strother et al., 1998). A recent study indicated that cocaine dose-dependently reduces the expression of messenger ribonucleic acid (mRNA) for circadian genes and increases messenger ribonucleic acid (mRNA) expression for melatonin receptors in embryonic zebra fish (Shang and Zhdanova, 2007). On the other hand, melatonin, the principle circadian hormone, was found to attenuate some cocaine effects. Both pre-treatment with melatonin and the physiologically elevated melatonin concentrations at night neutralized some cocaine effects upon gene expression and improved the survival rate (Shang and Zhdanova, 2007). The investigators hypothesize that the cocaine-induced developmental alterations might be mediated by a temporal dysregulation of intrinsic processes, and that melatonin might be of therapeutic value in the treatment of prenatal cocaine exposure.

A study that administered cocaine to pregnant sows found that exposed piglets had increased active sleep and reduced wakefulness during the first month after birth. Evidence from studies in humans has been conflicting. It has been suggested that newborns with prenatal exposure to cocaine spend more time awake, have more frequent arousals, more indeterminate sleep, increased SWS maturity and decreased spectral $\delta$ power. These findings need to be interpreted cautiously. The majority of studies did not adjust for other confounding variables such as education, socioeconomic status, social and physical environment, nutritional maintenance and general health of the mother, for the number of prenatal visits, birth weight and, notably, for prenatal exposure to alcohol, nicotine and other drugs. Positive correlations between cocaine exposure and lower birth weight, small number of prenatal visits and co-use of alcohol, tobacco and other drugs were noted in many of the sleep studies (e.g. DiPietro et al., 1995; Gingras et al., 1995; Regalado et al., 1995; Scher et al., 2000). Bendersky et al. (1996) found that more mothers who used cocaine during pregnancy had poorer living conditions and more frequently received public assistance.

In the study by Scher et al. (2000), the only PSG study that adjusted for sociodemographic covariates and exposure to alcohol, tobacco and marijuana, maternal cocaine use was significantly correlated only with reduced $\delta$ spectral power at birth, but not with differences in sleep stage percentages, total time awake, body movements or arousals. The reduction in $\delta$ spectral power persisted at one-year follow-up. There are no studies on the question of whether these alterations persist during childhood and adolescence and whether they have any clinical relevance.

The alarming prevalence of cocaine use among pregnant women, the intriguing results of preclinical studies on prenatal cocaine and the circadian clock, but also the obvious limitations of the studies in humans performed to date call for further research on the effects of prenatal cocaine upon sleep. It is necessary that the studies in humans adjust for the aforementioned covariates.
4.1.1.2. MDMA and MDE

There are only limited data on the acute effects of MDMA and MDE upon sleep. In agreement with subjective reports of users, studies have shown the stimulant effects of these substances, which resemble those of cocaine and amphetamine (Feinberg et al., 1974).

After MDE ingestion, wakefulness is increased markedly, and REM sleep is suppressed almost completely (Gouzoulis et al., 1992). Similar patterns of behavioral state were observed in a rat model of MDMA intake, and circadian rhythms remained disturbed for 28 days after a single dose of MDMA (Balogh et al., 2004). In humans, subjective sleep problems persisted for 48 hours after ecstasy use (Verheyden et al., 2003; Huxster et al., 2006).

The question of whether MDMA induces serotonin neurotoxicity in humans has become a field of extensive research (see chapter 1.2.2.4.). This hypothesis is confirmed by sleep studies. The two PSG studies of heavy ecstasy users analyzed in this review both show persistent alterations of the sleep profile in abstinent MDMA users. However they contradict one another with respect to the pattern of alterations. It is unlikely that SWS and SE are increased as suggested in the short abstract by McCann et al. (2000), taking into consideration the subjective reports of heavy ecstasy users. These individuals often complain of persistent sleep disturbances (Parrott et al., 2000; Dughiero et al., 2001; Verheyden et al., 2003). Hence, it would be much more in keeping with clinical experience that stage 2 sleep and TST are reduced, and that WASO and REM sleep percentage may be increased, as observed by Allen et al. (1993).

The findings of the study by Allen et al. (1993) were reproduced in a recent investigation by McCann et al. (2007). 25 young, abstinent ecstasy users were compared to 23 non-MDMA using controls. The extent of their previous exposure to MDMA (between 30 and 324 occasions) was similar to the earlier study. During baseline PSG recordings, ecstasy users had a tendency for reduced TST as well as significantly more stage 1 and less stage 2 sleep than controls. Sleep efficiency was reduced. There was a tendency for decreased REM sleep latency. Not reaching statistical significance, REM sleep percentage was higher in ecstasy users compared to controls. No data are given on phasic activity of REM sleep.

These findings are in remarkable accordance with PSG studies of experimental depletion of the serotonin precursor tryptophan, a test that induces serotonin deficiency. Studies have been carried out in healthy individuals (Voderholzer et al., 1998; Bhatti et al., 1998), in psychiatric patients (Moore et al., 1998; Riemann et al., 2002) and in both groups of subjects (Huwig-Poppe et al., 1999; Voderholzer et al., 2007). The bottom line of these studies is that tryptophan depletion is associated with a decrease in stage 2 sleep, in TST and in SE. Stage 1 sleep and wakefulness are increased. Phasic activity of REM sleep, measured as REM density or as number of eye movements, is enhanced. In addition to that, REM sleep latency may be reduced and REM sleep percentage increased.

The agreement of the sleep alterations after induced serotonin deficiency with the sleep patterns observed in abstaining heavy ecstasy users is impressive. It substantiates the hypothesis of MDMA-induced serotonin neurotoxicity in humans.
4.1.1.3. LSD

The studies that investigated the sleep effects of LSD present conflicting findings. All but two preclinical studies show that LSD increases wakefulness and suppresses REM sleep. Bilkova et al. (1971) apparently did not find any significant effects of LSD on behavioral state since LSD was administered subcutaneously and the recordings lasted for a short time only after the end of infusion. The study by Hartmann (1967) was the only study that administered a low dose of LSD in rats. Hence, there may be differences in LSD effects that are dose- and species-related.

The two studies in humans which assessed REM sleep performed EMG recordings only in a minority of subjects. EMG is an instrument which is crucial for the differentiation of REM sleep and desynchronized EEG activity during wakefulness. Only the study by Green (1969) found an increase in total REM sleep, yet this study, which was conducted in 1965, was flawed by serious methodological difficulties. Total REM sleep did not differ in the other study (Muzio et al., 1966), and the arousing effects of LSD were confirmed.

There is no publication of a sleep study of LSD that was conducted after 1968, according to the criteria by Rechtschaffen and Kales (1968). This surprising fact may be of heuristic value.

In the late 1960’s, any data showing that LSD increases REM sleep would have confirmed the LSD theory of dreaming and would have gained immense resonance. Such findings would have been revolutionary in that they would have indicated a common neurobiological mechanism from which both dreaming and LSD-induced psychotic phenomena may derive. This hypothesis was still relevant in 1983, when Fischman (1983) advocated a common serotonin-based substrate for dreaming, LSD hallucinations and schizophrenia. Hence, it is impossible to believe that all research concerning the effects of LSD upon REM sleep was abandoned simply for lack of interest after 1968. A substantial number of studies with LSD continued to be performed in humans for other purposes. All of the data from animal experiments conducted after 1967 are incompatible with REM sleep enhancing properties of LSD. The lack of published sleep studies in humans after 1968 may be interpreted as a hint for a relevant publication bias. Those studies that did not find an enhancement of REM sleep by LSD might not have been published, since they did not support the intriguing hypothesis.

Therefore, the remarkable discontinuation of publications makes the assumption more probable that LSD decreases REM sleep, as suggested by preclinical data.

According to recent research, there may in fact be a common neurophysiologic substrate for dreaming, LSD-induced hallucinations and schizophrenia. Aghajanian and Marek (1999b) have proposed a synaptic mechanism for LSD-induced hallucinations. LSD acts as a potent partial agonist at presynaptic serotonin 5-HT-2A receptors of excitatory neurons in the neocortex. Glutamate is released into the synaptic cleft, and excitatory postsynaptic potentials are evoked in layer V pyramidal cells. This release of glutamate occurs as the slow, “asynchronous” release which is initiated only about 50 milliseconds after action-potential mediated transmitter release (Aghajanian and Marek, 1999a). Hence, LSD promotes the late component of prolonged excitatory postsynaptic potentials in cortical pyramidal cells.
Serotonin itself does not evoke these asynchronous excitatory postsynaptic potentials. On the contrary, substances which elevate serotonin concentrations have been found to diminish the effects of hallucinogens (Bonson et al., 1996). It is speculated that this may be due to the inhibitory action of 5-HT-1 and other 5-HT-receptors. On the other hand, asynchronous excitatory postsynaptic potentials are enhanced when serotonin concentrations decline, e.g. during an experimental washout of serotonin. The lowest serotonin concentrations in healthy individuals occur during REM sleep (Portas et al., 2000). Hence, these asynchronous excitatory postsynaptic potentials in layer V pyramidal cells may also be responsible for the hallucinatory state experienced during dreaming.

Serotonin-mediated abnormalities in glutamatergic transmission have been proposed as the neurochemical correlate of schizophrenia (Aghajanian and Marek, 2000). A serotonin deficit similar to that observed during REM sleep may exist in schizophrenia. This hypothesis is confirmed by promising treatment strategies that have included serotonin reuptake inhibition in addition to dopamine receptor antagonism (Silver et al., 2000; Van Hes et al., 2003).

Gottesmann (2006) proposes a different model of the relationship between REM sleep and schizophrenia, stressing the similarities in dopamine release. LSD effects do not play a role in this theory.

During REM sleep, noradrenalin and serotonin activity reaches its lowest levels. Dopamine release is disinhibited (Gottesmann, 2002), and its activity in the nucleus accumbens reaches its highest levels. In the prefrontal cortex, dopamine release is decreased compared to the waking state. Furthermore, the glutamate concentration in the nucleus accumbens is reduced considerably during REM sleep. These same features are regarded as the key neurochemical correlates of schizophrenia.

The earlier hypothesis (Muzio, 1966; Torda, 1968; Fischman, 1983) linked LSD ingestion to a global increase in serotonin activity, and this global increase was assumed to be the substrate for both REM sleep and hallucinations. No one will gainsay that this theory is obsolete nowadays. Current neurophysiologic knowledge does not sustain that global increases in serotonin activity induce REM sleep, since REM sleep is a state of serotonin silence (Portas et al., 2000). Therefore, although there are still promising theories which assume a commonality between hallucinatory sequences during REM sleep, LSD effects and psychotic states, they do not presuppose that LSD enhances REM sleep: Aghajanian and Marek maintain that low levels of serotonin (as during REM sleep) evoke asynchronous excitatory postsynaptic potentials in a similar way as active stimulation of 5-HT-2A receptors (LSD). The theory by Gottesmann regards dopamine activity in the nucleus accumbens as the decisive mechanism for dreaming and schizophrenia, and leaves out the role of LSD.

4.1.1.4. Cannabis

The PSG studies of cannabis administration and withdrawal are heterogeneous due to differences in drug dosage, time and route of administration. Secondly, some studies are specific for Δ-9-THC, whereas in other studies Δ-9-THC and CBD effects are confounded. Thirdly, personal factors such as different degrees of prior experience with the drug, superposing tolerance or withdrawal effects, as well as individual expectations and emotional reactions modulate the sleep effects of cannabis.
Acute administration of Δ-9-THC affects SOL depending on the aforementioned factors. If a high oral dose of Δ-9-THC is given less than two hours before bedtime to marijuana-naïve subjects, SOL will probably be increased. On the other hand, a moderate dose ingested 2 to 3 hours before bedtime is likely to decrease SOL (Cousens and DiMascio, 1973). This would correspond to smoking marijuana about 30 to 45 minutes prior to bedtime (see chapter 1.2.4.3.). In an animal model, wakefulness is increased initially, before the hypnotic properties predominate. The sleep profile after Δ-9-THC intake is characterized by an increase in stage 4 sleep. Stage 3 sleep is reduced. There is a pronounced decrease in REM sleep: total REM sleep and REM density are reduced and REM sleep latency is increased. The sedative effects of cannabis may still be present in the morning (Nicholson et al., 2004). In agreement with these objective data, individuals often report greater ease in getting to sleep or improved sleep quality, and sometimes residual somnolence the morning after administration of Δ-9-THC.

When given in a higher dosage, CBD apparently acts predominantly as a sedative (Monti, 1977; Cunha et al., 1980). However, studies that employed lower doses of CBD demonstrated that after acute administration wakefulness is increased and REM sleep reduced (Murillo-Rodriguez et al., 2006; Nicholson et al., 2004).

When repeated doses of marijuana are administered, tolerance develops to SWS effects. Tolerance is less pronounced with respect to REM sleep effects. Accordingly, in a study of the changes in subjective marijuana effects over various years of use, consumers reported desirable effects upon sleep, such as more sleep or more restful sleep, less frequently than at the baseline interview (Halikas et al., 1985).

Upon withdrawal, sleep is often markedly disturbed. Sleep onset latency and time awake after sleep onset are increased. A short REM latency and increased REM sleep percentage as well as REM density give proof of an REM rebound.

Subjective sleep disturbances constitute one of the most frequently reported marijuana withdrawal symptoms, being apparent in about three fourths of all subjects who experience a withdrawal syndrome (Wiesbeck et al., 1996). Individuals often complain of difficulty falling asleep, of decreased depth of sleep and of strange dreams. These symptoms correspond to the increases in objective SOL, the reduction in total slow wave sleep and the REM rebound. Depending on the characteristics of the sample, such as age, frequency of cannabis use and treatment seeking status, between 30 and 45% of chronic users will experience moderate to severe sleep disturbances, and about 15 to 40% will experience moderate to severe strange dreams. Sleep disturbances usually begin within 48 hours of cessation. They generally persist for at least two weeks, but may not disappear by 45 days of discontinuation (Budney et al., 2003). Treatment of cannabis withdrawal with oral Δ-9-THC also improves sleep disturbances (Haney et al., 2004). The efficacy of this substitution treatment was replicated in a recent study by Budney et al. (2007).

A single study (Walther et al., 2006) demonstrated the effectiveness and tolerability of Δ-9-THC in the treatment of agitated behavior at night in dementia. No adverse effects were observed after ingestion
of Δ-9-THC. Nocturnal motor activity was reduced by 59% from baseline. In addition to that, other parameters such as appetite disturbances, irritability and anxiety improved as well.

Dementias of the Alzheimer and non-Alzheimer type produce annual costs of 148 billion dollars to U.S. government and business (Alzheimer’s Association, 2007). In patients suffering from advanced Alzheimer’s disease, circadian rhythm disturbances and agitation in the evening and at night can be observed in up to 50% (Hope et al., 1999). They constitute an important cause of long-term hospitalizations in patients. A systematic review revealed that treatment with atypical antipsychotics was superior to placebo only in less than two-thirds of the trials, and frequent adverse effects were encountered (Lee et al., 2004), possibly associated with an increase in mortality (Daiello, 2007). Co-administration of benzodiazepines is generally not recommended since it increases the risk of serious complications such as aspiration pneumonia (Daiello, 2007).

The limitations of the available treatment options warrant the search for effective and safe alternatives. Δ-9-THC appears to meet these criteria. Randomized, placebo-controlled studies with large sample sizes are needed in order to corroborate the preliminary findings.

The studies of sleep after prenatal exposure to cannabis were conducted well. They controlled for possible covariates such as demographical characteristics and maternal psychosocial variables, use of other substances and infant characteristics such as birth weight. They found that marijuana use during any trimester was associated with an increase in small and large body movements and a decrease in quiet sleep at birth. Cannabis exposure during the first trimester increased mixed active sleep at birth, decreased low voltage irregular active sleep and decreased the number of rapid eye movements. At the age of three years, the group of exposed children still had poorer sleep efficiency, increased WASO and more frequent arousals.

Hence, there is evidence that the induced changes in sleep patterns persist at least until the age of three years. It is an intriguing question for further research whether the observed sleep disturbance persists during later childhood and adolescence and what the clinical implications of the presented findings are. Children with sleep problems at the age of 3 to 5 (according to maternal reports) appear to have an increased propensity for early onset of alcohol, tobacco, marijuana and other drug use (Wong et al., 2004).

4.1.2. Effects of sleep disturbances upon propensity for drug abuse

There is evidence that sleep problems and drug abuse disorders often co-exist simultaneously in the same individual (Ford and Kamerow, 1989; Breslau et al., 1996; Vignau et al., 1997; Johnson and Breslau 2001). The well-conducted study by Johnson and Breslau (2001) exclusively addressed this question and analyzed data from a sample of almost 14000 adolescents. In the statistical analyses, the relationship between use of illicit drugs and trouble sleeping remained significant even when adjusting for age, sex, race, family income as well as, notably, internalizing and externalizing problems.

However, two studies of the prevalence of drug use which additionally examined the relationship to sleep problems or to sleep deprivation as a work condition did not detect a significant correlation
It has been pointed out that some particular details of these studies may have impeded statistical significance. The fact that in drug users sleep problems are more frequent is not an extraordinary observation. Psychiatric disorders are generally associated with higher rates of sleep disturbances. The substances of abuse have been shown to produce marked alterations of sleep patterns. Hence, studies which confirm their simultaneous co-existence do not answer the question of whether sleep disturbances predispose to substance use.

Since Ford and Kamerow (1989) and Weissman et al. (1997) analyzed the same data in similar ways, there are in fact only three different studies which investigated the relationship between preexisting sleep problems and subsequent onset of drug abuse. The results are conflicting. The studies by Ford and Kamerow (1989) and Weissman et al. (1997) did not detect a greater incidence of drug abuse disorders among individuals with sleep problems. The odds ratio for new onset of drug abuse yielded a non-significant 1.9 in individuals with insomnia at the first interview. Parenthetically, this odds ratio was only adjusted for age, sex and site, and not for other demographic or for psychopathological variables. However, it needs to be taken into account that the mean age of the participants was 48 years (Weissman et al., 1997). At this age, new onset of a drug abuse disorder is rare. Also, individuals were reinterviewed already within one year.

Breslau et al. (1996) examined data from adults of a more relevant age (21 to 30 years) and there was an interval of 3.5 years between interviews. The investigators found impressive odds ratios both for insomnia and hypersomnia (7.2 and 13.4, respectively; both significant). However, the odds ratios were adjusted only for gender. Correction for other variables would have been necessary. Demographical characteristics such as unemployment as well as not being married (Ford and Kamerow, 1989), but also numerous psychiatric disorders have been shown to be associated with a higher prevalence of sleep problems: alcohol abuse, nicotine dependence (Breslau et al., 1996), attention deficit/hyperactivity disorder (Philipsen et al., 2006), conduct problems (Chervin et al., 2003), schizophrenia and bipolar affective disorder (Berger, 2004). On the other hand, associations between these same factors and drug abuse have also been demonstrated: the aforementioned demographical characteristics unemployment and not being married (Merline et al., 2004) as well as the above cited psychiatric disorders alcoholism and attention deficit/hyperactivity disorder (Rounsaville, 1991), but also schizophrenia, bipolar affective disorder, nicotine dependence and conduct disorders (Berger, 2004).

Therefore, although the study by Breslau et al. (1996) observed the temporal relationship that young persons with insomnia or hypersomnia are more likely than good sleepers to develop a drug abuse disorder in subsequent years, it did not establish an independent correlation or even a causal relationship. Since it did not control for variables that are associated with a higher prevalence of both sleep problems and possibly of drug abuse, it cannot be ruled out that sleep problems and drug abuse merely constitute epi-phenomena of other conditions. For instance, if unemployment is responsible for a greater risk to develop a sleep disorder and also for a greater risk to develop a drug abuse disorder, then these two disorders, despite a tendency to occur in the same individual, might still be totally independent of one another. This is why the adjustment for the relevant covariates is indispensable in
this kind of an investigation, and the failure to perform these produces very impressive, but unreliable results.

The study by Wong et al. (2004) found that overtiredness and any sleep problem at ages 3 to 5 was positively correlated with onset of drug use by age 12 to 14. This relationship remained significant when adjusting for attention problems, aggression, depression and anxiety. However, the study sample consisted of Caucasian boys only, and the majority was from alcoholic fathers. Sleep problems at ages 3 to 5 were assessed by the mothers' ratings of “overtiredness” and “trouble sleeping”. The early onset of drug use is not necessarily correlated with subsequent drug abuse or dependence, although such a relationship exists for alcohol (Grant and Dawson, 1997).

The odds ratios in the study by Breslau et al. (1996) suggest that the relationship between preexisting sleep disturbances and subsequent drug abuse might be even more intimate than the presumed association between sleep problems and alcohol abuse as well as other psychiatric disorders. These promising preliminary findings, but also the demonstrated weaknesses of the available studies warrant extensive research in this area, performed as prospective studies which adjust for all of the aforementioned variables, which are supposed to be related to both sleep problems and the propensity for drug abuse.

There have been no studies of the predictive value of objective sleep disturbances for treatment outcome in abstinent cocaine- or marijuana-dependent patients. The question of whether these have a similar importance as in alcoholic patients (see chapter 1.1.) remains unanswered. Hence, there is a great need for prospective studies which assess objective and subjective sleep measures during cocaine and marijuana withdrawal and investigate the relationship to treatment outcome.

There is conflicting evidence with respect to the predictive value of dream characteristics in abstinent cocaine users. One study suggested that frequency of drug dreams during the first month of abstinence was correlated positively with relapse by the follow-up interview at eight months (Christo and Franey, 1996). Drug dreams at follow-up were correlated positively with craving and with sleep disturbances at follow-up. The other study (Reid and Simeon, 2001) only found a tendency for relapse more often in those patients who experienced urges after drug dreams during the first month. Both studies are in agreement that drug dream frequency increases upon withdrawal, but subsequently declines with continued abstinence. After relapse, drug dream frequency is low.

4.2. Limitations of this review

A systematic review, albeit more objective and comprehensive than a simple review, still may not identify the totality of all relevant studies. This lack of completeness may be due to publication bias, since studies which do not find significant relationships are less likely to be published, or might be published in journals that are not registered in the electronic databases. It has been shown (chapter 3.1.1.) that at least three articles were not identified by the database searches since they were published as short abstracts only. Furthermore, studies that found no impact of a recreational drug upon sleep, but that were published for other significant findings, may have escaped the database searches. The study by Foltin and Fischman
(1997) serves as an example. It was published for the cocaine effects e.g. on mood and craving, but it was not registered by the database searches due to the lack of observed sleep effects. It was identified when screening the reference lists of eligible articles. Also, this review only included articles written in four different languages. It cannot be ruled out that relevant studies, e.g. with non-significant findings, were published in national journals, in a language other than English, German, French or Portuguese. Therefore, on the whole, it needs to be assumed that this review may consider a disproportionately large number of studies which found statistically significant results.

It has been pointed out that some articles were not identified due to more or less inevitable limitations of the chosen key words. This occurred for those articles that considered sleep disturbances only as one minor aspect of adverse drug effects or withdrawal symptoms. It also occurred when drug dependence was regarded only as a minor psychiatric disorder compared to others that are possibly related to sleep disturbances. Two articles, which were included only ex post when screening the reference lists, would have been identified if the key words had included “drug abuse” and “dream”. The inclusion of these key terms would have been reasonable. However, it needs to be held in mind that the database searches performed in the present review already yielded a total number of 1200 studies.

Even when performed according to pre-defined criteria, the study selection in a systematic review cannot be detached entirely from subjective elements. This applies even more when the study selection is made by a single investigator only.

The quality of a review depends on the quality of the studies assessed. Unfortunately, the quality of the available data is much inferior to studies from other fields of medicine. A considerable portion of the analyzed studies was conducted and published in the last decades of the past century and not according to current methodological standards.

In addition to that, there are a large number of rather inevitable methodological difficulties associated with research in this field. These are mentioned in detail in chapter 3.1.2. (“Quality assessment”). Due to the ethical problem of administering substances of known harmfulness to normal subjects from the general population, few of the relevant studies were performed in drug-naïve subjects, and only a subgroup of these included healthy individuals (e.g. Gouzoulis et al., 1992; Muzio et al., 1966; Kales et al., 1972; Tassinari et al., 1976). Randomization, a key methodological principle, could be realized only in very few studies, e.g. with therapeutical cannabis. However, it is only by randomization that many of the commonly encountered methodological problems could be avoided. Randomized samples would reduce the impact of other factors that potentially modulate sleep. Examples for these factors are co-use of further psychoactive substances, psychiatric comorbidity and preexisting sleep abnormalities (see chapter 3.1.2.). Furthermore, some studies depend on the individuals’ substance use histories. These are not always reliable, owing to recall bias and social desirability. Crucial study regulations, such as prevention of daytime napping and rules on the use of psychoactive substances during the course of the study, are very difficult to enforce.

The completeness of the studies included in the meta-analyses may have been compromised by the above-cited difficulties of the database searches, such as publication bias, language bias and
subjectivity of study selection. Although these studies were conducted relatively well, they were still flawed by some of the cited methodological problems. The studies’ findings were not published adequately for statistical exploitation according to current standards. Therefore, the meta-analyses were performed on the basis of a number of premises. Although it was attempted to make only conservative assumptions, it cannot be ruled out that the statistical models distorted the actual conditions.

With respect to the heterogeneity between studies, it needs to be considered that a few subjects in the studies by Gillin et al. (1994) and Thompson et al. (1995) were dependent on methamphetamine, and not on cocaine. Also, there are probably some differences between studies regarding psychiatric comorbidity, co-use of other drugs and extent of prior cocaine use. In the studies by Gillin et al. (1994) and Thompson et al. (1995), acute withdrawal was regarded to be, instead of nine, the initial eight and ten days of abstinence, respectively. It can also be objected that the number of subjects was not identical for all studies and that not all studies provided data on all sleep measures. However, an important aspect is that the same instrument (PSG) was employed to measure the outcomes in all trials. I-square statistics indicated that heterogeneity between studies was not considerable.

Sleep continuity and architecture measures are not Gaussian distributed. The data for the pre-post design were not given as individual values for each subject. Instead of differences between early and late abstinence for each individual, the group mean values for each phase were considered as dependent variables. In the study by Thompson et al. (1995), the data for early and late abstinence are derived from different subjects, according to an independent two-group design. In the studies by Kowatch et al. (1992) and Gillin et al. (1994), there were considerable rates of drop-outs. Here, the available data were assumed to be representative.

In various articles, only roughly rounded values for the standard deviations are provided. The reported standard deviations were pooled assuming an intraindividual correlation of $r=0.5$. When standard deviations were not given, the highest standard deviation from the other studies was imputed. Since no standard deviations for SWS percentage were provided in any study, a conservative standard deviation of 5% was imputed, i.e. 95% of the data points were assumed to be in the range of ±10% of mean values.

This review has laid bare the weaknesses of the available studies on the relationship between illicit recreational drugs and sleep. Yet, the findings need to be interpreted constructively. The present review attempts to provide the most reliable information to date on this relationship. It defines the current state of knowledge and indicates where future research is needed the most.
5. Summary

This systematic review on illicit recreational drugs and sleep investigated the effects of cocaine, MDMA, MDE, LSD and cannabis upon subjective and objective measures of sleep, both after drug administration and during withdrawal. It also examined whether, on the other hand, sleep disturbances affect an individual’s propensity to use these drugs. The electronic databases Medline, Embase, CINAHL, PsycINFO and Psyndex were searched for all studies on these substances in conjunction with sleep, and reference lists of eligible articles were screened for further relevant studies. Articles published until October 2006 were eligible. 88 out of a total of 1200 studies were identified for analysis and twelve further studies were added when scrutinizing the reference lists. Meta-analyses were performed only for cocaine withdrawal, since number, quality and homogeneity of the other studies did not permit such analyses.

This dissertation has revealed the limitations of the available data. Studies have been flawed by a large number of methodological difficulties, some rather inevitable, some due to less rigorous standards of methodology in the past decades. It has been pointed out where future research is needed the most.

Acute administration of cocaine, MDMA and MDE increases wakefulness and suppresses REM sleep. These substances share a common pattern of acute effects on sleep with other psychostimulants such as amphetamine. LSD may have similar acute effects, but there is conflicting evidence.

In patients withdrawing from cocaine, sleep continuity measures resemble those of primary insomniacs. Even in the absence of depressed mood, REM sleep latency is not much longer than in depressed patients. After the first ten days of abstinence, sleep continuity measures deteriorate even further. Interestingly, the patients do not recognize this deterioration. It is accompanied by a worsening in cognitive performance.

Heavy ecstasy users often complain of persistent sleep disturbances. PSG studies have indicated that in abstaining heavy ecstasy users, stage 2 sleep, TST and SE are reduced. These findings can be interpreted as related to MDMA-induced serotonin neurotoxicity in humans.

Acute administration of Δ-9-THC increases stage 4 sleep and reduces REM sleep. After repeated administration of marijuana, tolerance develops to SWS effects. Upon withdrawal, SOL is elevated, SE is reduced and an REM rebound can be observed. Sleep disturbances constitute one of the most frequently reported symptoms of cannabis withdrawal. There is evidence suggesting that Δ-9-THC can be a treatment alternative for circadian rhythm disturbances, e.g. in patients with dementia and nighttime agitation.

Although some studies have shown that in patients with sleep disturbances the prevalence of drug abuse is elevated and that the incidence of new onset of an illicit drug use disorder is increased, an independent correlation or even a causal relationship has not been established. No studies have been conducted that investigated the predictive value of objective sleep disturbances during cocaine and cannabis withdrawal for treatment outcome. There are limited data on the predictive value of drug dreams during cocaine withdrawal.
6. Zusammenfassung


Ein Hauptanliegen dieser Dissertation ist es, die zahlreichen methodologischen Mängel der vorliegenden Studien aufzudecken und zu bewerten. Dabei wird darauf hingewiesen, wo in Zukunft weitere Forschung nötig ist und wie diese durchgeführt werden sollte.

Kokain, MDMA und MDE zeigen bei akuter Verabreichung eine wachheitsfördernde und REM-Schlafunterdrückende Wirkung, wie sie auch für anderen Psychostimulanzien, zum Beispiel Amphetamin, bekannt sind. Es liegen widersprüchliche Daten zu der Frage vor, ob auch LSD eine solche akute Wirkung auf den Schlaf hat.


Obwohl einige Studien gezeigt haben, dass bei Patienten mit Schlafstörungen sowohl die Prävalenz als auch die Inzidenz von Drogenmissbrauch erhöht sind, konnte keine unabhängige Korrelation oder gar ein kausaler Zusammenhang nachgewiesen werden. Zum prädiktiven Wert von Träumen für die Rückfallwahrscheinlichkeit während des Kokainentzugs liegen einzelne widersprüchliche Daten vor.
### 7. References


Aghajanian GK, Marek GJ (1999b) Serotonin and hallucinogens. Neuropsychopharmacology 21(2 Suppl):16S-23S.


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