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Sleep Abnormalities During Abstinence in Alcohol-Dependent Patients

Aetiology and Management

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Contents

Abstract

Virtually every type of sleep problem occurs in alcohol-dependent patients. Typically, these individuals take a longer time to fall asleep and show decreased sleep efficiency, shorter sleep duration and reduced amounts of slow wave sleep when compared with healthy controls. Their sleep patterns are fragmented, and the typical time course of electroencephalogram (EEG) delta wave activity is severely disrupted. The amount of rapid eye movement (REM) sleep may be reduced or increased. Sleep changes can persist during months or years of abstinence, and recent studies indicate that certain alterations in sleep architecture, as well as subjective sleep complaints, predict relapse to alcoholism.

The mechanisms of action of short and long term alcohol administration on sleep are incompletely understood. They may arise from an interaction with γ-aminobutyric acid (GABA), serotonin (5-hydroxytryptamine; 5-HT), adenosine or other neurotransmitter systems.

While only a few pharmacological and nonpharmacological strategies to im-

prove or normalise disturbed sleep in individuals who have recovered from alcoholism have been studied, the use of benzodiazepines, other hypnosedatives or selective serotonin reuptake inhibitors is not recommended. Therapies include sleep hygiene, bright light therapy, meditation, relaxation methods, and other nonpharmacological approaches.

Further studies are needed to clarify the relationship between sleep, sleep abnormalities and alcoholism, and to establish new approaches to improve sleep in alcohol-dependent patients and to prevent withdrawal reactions that affect sleep during abstinence.

Severe sleep disturbances are common in alcohol-dependent patients. Virtually every type of sleep disorder – insomnia, hypersomnia, circadian rhythm sleep disorders (e.g. phase advance or phase delay of sleep period) and parasomnias (e.g. nightmares, sleep walking, enuresis) – may occur in alcohol-dependent patients during periods of drinking, withdrawal and abstinence (see Gillin and Drummond[1] for recent review).

Sleep disturbances play an important role in the diagnosis and treatment of alcoholism, and accumulating evidence suggests that objective and subjective alterations of sleep during abstinence may predict relapse in the future. Specifically, prolonged sleep latency, enhanced propensity for rapid eye movement (REM) sleep, low amounts of deep non–REM sleep and reduced sleep efficiency at different stages of abstinence are among the best predictors of treatment outcome in alcohol-dependent patients.[2-5] Moreover, patients complaining of abnormal sleep with difficulties in falling asleep are more likely to relapse than those with better subjective sleep quality.[2,6] Some alcohol-dependent individuals may resume drinking in an attempt to self-medicate their sleep problems.[7,8] The normalisation and subjective improvement of sleep during abstinence might, therefore, prevent resumption of drinking in at least this subset of patients.

Unfortunately, the aetiology and treatment of alcohol-related sleep disturbances are not well understood, and there are no widely accepted therapeutic guidelines.[9,10] In this article, we aim to provide an overview of possible interventions to improve sleep in patients recovering from alcoholism. We first describe the salient features of normal sleep architecture and the sleep electroencephalogram (EEG). We then summarise the effects of alcohol on sleep variables, the sleep EEG, sleep-related breathing and periodic leg movements during sleep in healthy individuals and in alcohol-dependent patients. Next, we discuss the effects of alcohol on neurochemical systems which are thought to play a role in the regulation of sleep. And, finally, we outline currently available pharmacological and nonpharmacological treatment options to improve disturbed sleep in abstinent alcohol-dependent individuals.

1. Sleep Stages and the Sleep Electroencephalogram (EEG) in Healthy Individuals

Characteristic changes in brain electrical activity, i.e. the EEG, serve to discriminate between wakefulness and sleep. The typical ≈10Hz alpha rhythm of quiet wakefulness changes to a pattern of theta frequencies (≈5 to 8Hz) during the onset of sleep (stage 1; fig. 1). Deeper sleep is characterised by the occurrence of phasic events such as sleep spindles (≈11 to 15Hz, sigma frequency range) and K-complexes (large regular potentials), as well as the presence of high amplitude slow waves with a frequency of ≈0.5 to 2Hz (delta frequency range). Standardised criteria are applied to subdivide polysomnographic recordings of EEG, electro-oculogram (EOG) and electromyogram (EMG) into wakefulness, REM sleep and non–REM sleep.[11] Based on the preponderance of slow waves, non–REM sleep is further subdivided into stages 2 to 4. Undisturbed sleep in healthy adults consists of four or more consecutive non–REM/REM sleep cycles

with a periodicity of approximately 60 to 100 minutes.[12]

Computer-aided decomposition of the sleep EEG reveals functionally distinct components. Slow wave activity (SWA; spectral power within 0.75 to 4.5Hz) is thought to represent a physiological marker of non–REM sleep intensity.[13,14] After sleep onset, SWA builds up rapidly in the first non–REM sleep episode and reaches a plateau during stage 4 (fig. 1). Shortly before REM sleep, it declines sharply and remains low until it increases again in the second non–REM sleep period, where it normally reaches a lower plateau value than in the first non–REM sleep episode. The global declining trend of SWA across consecutive non–REM sleep episodes reflects the sleep-wake dependent or homeostatic facet of sleep regulation.[14-16] Accordingly, SWA is enhanced after sleep deprivation and reduced after a daytime nap.[13,17]

In addition to SWA, EEG power in the frequency range of sleep spindles also underlies homeostatic influences. However, spindle frequency activity (SFA; spectral power within 12 to 15Hz) does not decline in the course of a nocturnal sleep episode, yet is reduced after sleep deprivation.[13,18,19] It shows a complex relationship to SWA and undergoes a characteristic modulation over the non–REM/REM sleep cycles. Highest values are seen at the onset and termination of non–REM sleep episodes, whereas the lowest values occur in REM sleep (fig. 1).

2. Effect of Alcohol on Sleep and the Sleep EEG

2.1 Healthy Individuals

It has long been known that alcohol, when given to healthy volunteers at bedtime, tends to shorten sleep latency, reduce the amount of REM sleep and prolong the duration of non–REM sleep.[20-25] Because alcohol is metabolised rapidly,[23,26,27] these changes in sleep architecture are typically confined to the first half of the night, and nocturnal withdrawal effects may disturb sleep towards the end of the sleep episode.[22,25] Specifically, late sleep may be shallow and interrupted by frequent awakenings, the amount of REM sleep may be increased, and dream recall or nightmares may be frequent. Moreover, activation of the sympathetic nervous system may induce tachycardia and sweating,[23] and gastric irritation, headache or a full

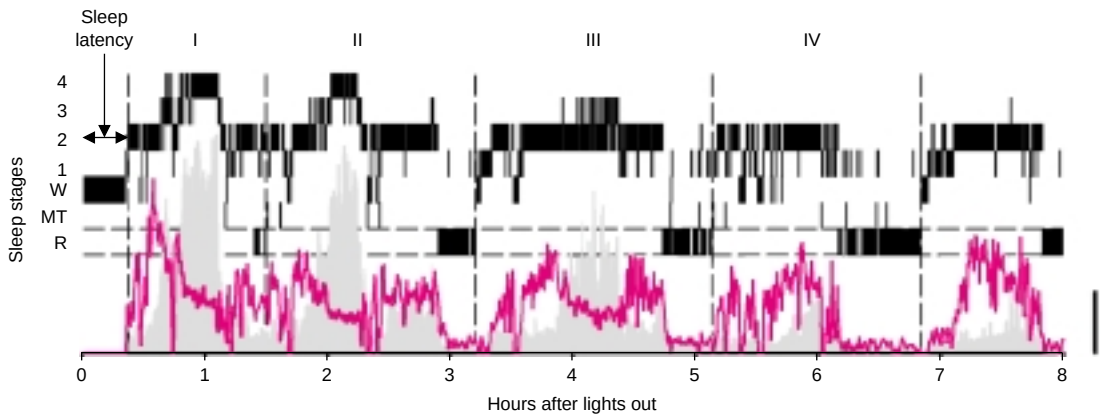

Fig. 1. Sleep stages and electroencephalogram (EEG) slow wave activity (SWA; power within 0.75 to 4.5Hz; grey bars) and spindle frequency activity (SFA; power within 12.25 to 15Hz; blue line) during an 8-hour sleep episode in a young healthy man. 20-second epochs of W and MT were excluded for calculation of SWA and SFA. The calibration mark at the right of the x-axis represents 300 μV^2/Hz of SWA and 10 μV^2/Hz of SFA, respectively. Roman numerals at the top of the figure indicate consecutive non-REM/REM sleep cycles. **1**, **2**, **3**, **4** = non–rapid eye movement (REM) sleep stages; **MT** = movement time; **R** = REM sleep; **W** = waking.

bladder may occur, all of which cause repeated sleep interruptions.

While alcohol is commonly used by individuals with sleep disorders in an attempt to self-medicate, it can be seen that this is not appropriate and in fact counterproductive. Indeed, the International Classification of Sleep Disorders (ICSD) lists 'alcohol-dependent sleep disorder',[28] which occurs typically in patients with insomnia who do not have a diagnosis of alcoholism and who use alcohol as a bedtime sleeping aid for >30 days. Characteristic symptoms include restlessness and nocturnal awakenings with sweating, headache, dreams and dry mouth.[1]

The alcohol concentration in plasma may reach higher levels in older people than in young adults, especially in men,[29,30] and in these individuals sleep after alcohol consumption may be most strongly affected. For example, the consumption of 0.55 g/kg bodyweight of alcohol in the late afternoon (at 1700h) produced a maximum breath alcohol concentration of ≈0.9 mg/L in 10 healthy late middle-aged men (mean age of 62 years).[27] Breath alcohol levels were zero at the beginning of the sleep episode at 2300h. Nevertheless, individuals perceived their sleep as more superficial when compared with a control situation (i.e consumption of mineral water). Sleep efficiency, total sleep time and the duration of REM sleep and stage 1 were decreased. In the second half of the night, wakefulness was doubled. These data demonstrate that early evening alcohol consumption can disrupt sleep in men who are not alcohol-dependent at a time when the breath alcohol concentration has fallen to undetectable levels.

In the same study, EEG power densities in low delta frequencies were enhanced in non–REM sleep and REM sleep after alcohol consumption when compared with the control situation.[27] The most prominent changes occurred in slow wave sleep (SWS, stages 3 and 4), in which activity was increased in the delta, alpha and sigma bands. While these sleep EEG effects demonstrate a central action of alcohol at a time when the substance can no longer be detected, their physiological significance remains to be established.

In an earlier study involving 8 young adults, alcohol-induced changes during sleep were found to persist for longer than 24 hours.[31] The changes consisted of enhanced EEG power within the delta and alpha bands in SWS and were very similar to those in the older men after late afternoon alcohol consumption.

Furthermore, alcohol intake in the morning was reported to lead to sedation and impaired performance in divided attention and simulated automobile driving tasks in the afternoon, at a time when the alcohol concentration in breath in 12 healthy young men was approaching zero.[32] Interestingly, performance impairment appeared to be more pronounced after partial sleep deprivation (4 hours) than after a normal night of sleep (8 hours). These results suggest that the sedative effects of alcohol may arise from an 'unmasking' of a previously present sleep deficit. This finding is especially relevant for individuals with a high level of sleepiness (e.g. patients with sleep disorders or sleep apnoea, shift workers, or people with jet lag) in whom the impairing effect of alcohol may be enhanced, and the risk for alcohol-related automobile accidents may be increased.

2.1.1 Sleep-Related Breathing and Periodic Leg Movements

Superficial, shallow, nonrefreshing sleep with frequent arousals may be caused by disturbances of breathing and motor control during sleep.[28] For example, sleep apnoea or hypopnoea (repeated cessation or significant reduction of breathing for more than 10 seconds), restless legs syndrome (RLS) and periodic limb movements of sleep (PLMS) may prevent sleep or arouse an individual from sleep.

In 10 non-obese healthy men with no history of snoring or disturbed sleep-related breathing, alcohol enhanced snoring and upper airway resistance during sleep.[33] This may be related to an alcohol-induced selective inhibition of upper airway motor activity and concomitant increase in total inspiratory resistance.

A higher prevalence of sleep apnoea and/or hypopnoea than in controls (n = 20) has been observed in individuals with chronic alcoholism (n = 24) despite 3 to 6 weeks of abstinence.[34] Additionally, in a large sample of 643 men and 341 women attending a general sleep disorders centre, the likelihood of having PLMS was significantly higher in patients who consumed 2 or more alcoholic drinks per day than in those who did not.[35]

These detrimental effects of alcohol on sleep-related breathing and PLMS may cause excessive daytime sleepiness and fatigue during the day in otherwise healthy individuals or persons with mild upper airway restriction or pre-existing sleep apnoea or PLMS.

2.2 Alcohol-Dependent Patients

As alcoholism develops, patients often report that they are unable to sleep without a drink. Long term ingestion of alcohol, however, typically leads to a loss of SWS and SWA, and disruption and fragmentation of sleep patterns. When compared with age- and gender-matched controls in polysomnographic studies, alcohol-dependent patients showed prolonged sleep latency, decreased sleep efficiency, shorter sleep duration, reduced amount of SWS, and increased percentage of REM sleep.[36] In some patients, the normal rest-activity cycle may be disrupted. They can develop so-called 'polyphasic sleep-wake behaviour' with short, alcohol-induced periods of sleep and short periods of wakefulness (especially with binge drinking).[37]

According to their belief that alcohol improves sleep, some alcohol-dependent patients may continue drinking or resume drinking after abstinence in an attempt to avoid insomnia.[8] Few studies have examined the effect of acute alcohol intake on the sleep of alcohol-dependent individuals while they are actually drinking. Early studies suggested that alcohol promotes SWS initially.[38] Repeated use, however, may lead to rapid tolerance to this effect.

2.2.1 Alcohol Withdrawal

The severity of sleep disturbances during alcohol withdrawal varies, probably with the degree of physical dependence, as well as factors such as general health, nutritional status, past history of alcoholism and delirium tremens (DTs). In less severe withdrawal, unmedicated patients may experience symptoms of hyperarousal and jitteriness, and 3 to 5 days of altered sleep patterns with fragmented, shallow, short sleep episodes, often with increased amounts of REM sleep.[37,39-41] Since alcohol, particularly in large quantities, may suppress REM sleep, the elevated amounts of REM sleep during withdrawal may be viewed as a 'REM sleep rebound'. During DTs, sleep duration can be dramatically curtailed and fragmented, and REM sleep may be increased. Some patients may experience prolonged periods of sleep, so-called 'terminal sleep', while coming out of an episode of DTs.[42,43]

By the end of 1 to 2 weeks of abstinence, most patients show a slow improvement in sleep latency, sleep efficiency and total sleep time, and reduced wake time after sleep onset (WASO).[39-41,44] Nevertheless, at an average of 17 days post-abstinence, sleep efficiency, total sleep time and SWS were significantly reduced in 31 relatively healthy, 'pure' primarily alcohol-dependent individuals (i.e. without comorbid diagnoses such as depression) compared with those in 34 controls.[45] Sleep latency and REM density (a measure of ocular activity during REM sleep) were increased. While stage 4 sleep declines with age in both healthy controls and alcohol-dependent individuals, the decline was premature in the patients. i.e. young alcohol-dependent individuals showed sleep patterns similar to those of much older normal controls.

Depression and Sleep Disturbances

During the first weeks of withdrawal, many alcohol-dependent individuals experience depressed mood, and a sizeable number, perhaps 15 to 25% in an inpatient alcohol treatment ward, meet diagnostic criteria of a major depressive episode.[46] Fortunately, this episode usually abates within a few weeks without specific antidepressant therapy.[46] Many of these depressed patients have never had a prior episode of depression in the absence of drinking. Patients who first experience a major depres-

sive episode during withdrawal have been described as having 'secondary depression'.[47-49]

Alcohol-dependent patients who have secondary depression share many of the polygraphic sleep abnormalities traditionally associated with a primary major depressive disorder.[36] In addition to the subjective complaints of insomnia, they frequently show short REM sleep latency, decreased SWS, sleep efficiency and total sleep time, and increased WASO and REM density during the first month of withdrawal compared with nondepressed alcohol-dependent individuals and healthy controls.[45,50,51] Furthermore, although alcohol-dependent individuals with secondary depression are not usually as severely depressed as individuals with primary depression, as measured with the Hamilton Rating Scale of Depression, their objective sleep changes are often as prominent as, if not more so.[50,51] For instance, the percentage of REM sleep can be higher and SWS lower in depression secondary to alcoholism than in primary depression.

2.2.2 Abstinence

Abnormal sleep patterns in alcohol-dependent patients persist for months to years during recovery and abstinence. Even 1 to 2 years after drinking has stopped, sleep tends to be short and fragmented. Thus, total sleep time of 9 abstinent patients was just barely within normal age-matched limits at 14 months of sobriety.[5] Moreover, the percentage of sleep spent in SWS, as well as REM sleep latency, were still low after more than 1 year of abstinence. In 4 patients who were studied after an average of 27 months of abstinence, REM sleep percentage remained elevated and REM sleep latency short compared with healthy controls. These recent findings corroborate earlier observations by Williams and Rundell,[52] who reported objective sleep abnormalities after about 2 years of abstinence.

3. Mechanism of Action of Alcohol

Alcohol has long been thought to exert its pharmacological actions via an unspecific increase in the lipid fluidity of neuronal membranes ('the lipid theory of alcohol action'). Recent evidence, however, suggests that the substance can selectively modulate neurochemical processes in discrete regions of the CNS.[53,54] Its effects on sleep may arise from an interaction with lipophilic domains of γ-aminobutyric acid (GABA), serotonin (5-hydroxytryptamine; 5-HT), adenosine, glutamate, acetylcholine or glycine receptors.[54] Some of these neurotransmitters and neuromodulators may play important roles in the regulation of vigilance and sleep.[55-63]

To gain better insights into the neurochemical mechanisms underlying the effects of alcohol on sleep, these effects can be compared to the effects of compounds which have a known mechanism of action and affect these neurotransmitter systems selectively. For example, benzodiazepines (BDZs) and their analogues are thought to influence sleep and the sleep EEG by potentiating the inhibitory action of GABA at $GABA_A$ receptors.[61,62] Similar to alcohol, BDZs promote the onset of sleep, increase the duration of non–REM sleep and, at high doses, reduce the amount of REM sleep. They cause characteristic changes in the sleep EEG, which include the reduction of power in delta and theta frequencies and the promotion of sleep spindles. These distinct EEG changes have been referred to as the 'spectral GABA-BDZ signature'.[64]

Partially similar effects have been reported after melatonin administration before a daytime nap, at a time of day when endogenous melatonin levels are low.[65] These findings are in accordance with data in rats, which indicate that melatonin may enhance GABAergic activity at $GABA_A$ receptors.[66] Alcohol may or may not potentiate GABAergic neurotransmission.[54] Because alcohol increases delta frequencies in non–REM and REM sleep,[27,31] it appears unlikely that its effects on sleep are mediated by agonistic modulation of $GABA_A$ receptors.

Recent studies have shown that in contrast to the BDZs and analogues, structural GABA agonists such as muscimol and 4,5,6,7-tetrahydroisoxazolo-[4,5-c]pyridin-3-ol (THIP) and the GABA uptake inhibitor tiagabine increase SWS and SWA and reduce power in the frequency range of sleep spindles.[67-69] These effects resemble those of alcohol

more closely than those of the BDZs. Moreover, they are very similar to those of other compounds which inhibit serotonergic neurotransmission. Specifically, like alcohol,[27,31] single doses of THIP,[68] the 5-HT_{1A} receptor agonist ipsapirone (which probably leads to decreased neuronal activity at serotonin 5-HT_2 receptors),[70] and the 5-HT_2 receptor antagonists seganserin[71] and SR 46349B[72] enhance low delta frequency activity in non–REM sleep. These findings are in accordance with *in vitro* studies indicating that low concentrations of alcohol potentiate muscimol- and GABA-stimulated $GABA_A$ receptor function in isolated cortical membranes and cell preparations of rats and mice.[73,74] In addition, alcohol inhibits a serotonin-activated chloride current in 5-HT_{2A} receptors.[75]

The similar sleep EEG changes induced by alcohol, tonic $GABA_A$ receptor activation and 5-HT_2 receptor inhibition may reflect a common effect on sleep EEG power spectra. In this context it is interesting to note that recent studies in cats indicate that serotonergic cells of dorsal raphe nuclei may be under the tonic inhibitory influence of GABAergic neurons throughout the sleep-wake cycle.[76]

Pharmacological stimulation of adenosine receptors in rats is followed by enhanced delta frequency activity in non–REM sleep and suppression of REM sleep.[77,78] These effects resemble the initial effects of alcohol and are in accordance with the notion that alcohol inhibits uptake of extracellular adenosine from the interstitial space.[79,80] In contrast, low doses of the adenosine receptor antagonist caffeine prolong sleep latency, reduce low delta EEG frequencies, and enhance power in the frequency range of sleep spindles.[81,82] These changes may be similar to the alcohol-induced changes in later parts of the night.[27] Taken together these data indicate that alcohol may affect sleep and the sleep EEG via adenosinergic mechanisms. Nevertheless, the potency of alcohol to inhibit adenosine transport in hippocampal brain slices is low,[83] and its effects on intermittent wakefulness after sleep onset differ from those of caffeine.[27,81,82]

Apart from the classical neurotransmitters and their receptors, the growth factor and cytokine systems in the brain may be prominently involved in the physiological regulation of sleep.[55,84] For example, a highly reproducible pulse of growth hormone (GH) secretion occurs with SWS, indicating that GH-releasing hormone (GHRH) may be involved in the control of these processes.[85] Moreover, the GABA metabolite γ-hydroxy butyrate (GHB) and the 5-HT_2 receptor antagonist ritanserin induce a simultaneous enhancement of GH secretion and SWS and SWA during the initial hours of sleep.[86,87] In contrast, short and long term alcohol intake in individuals who are not alcohol-dependent produces a prominent reduction in the nocturnal SWS-related GH pulse.[88] Moreover, insulin-induced release of GH during wakefulness remained below control values for several days of abstinence in alcohol-dependent patients.[89]

4. Treatment of Alcohol-Induced Sleep Disturbances

Persistent sleep disturbances such as delayed sleep onset, frequent awakenings and reduced amounts of SWS during abstinence are among the difficulties that may challenge the successful treatment of alcoholism.[45,90] Recent data indicate that an increased propensity for REM sleep, prolonged sleep latency, reduced sleep efficiency, and subjective sleep complaints at different stages of sobriety can predict early relapse to drinking (see Gillin and Drummond[1] for review). The attempt to normalise alcohol-related sleep changes may, therefore, improve therapeutic outcome in some patients.

Sleep disturbances following alcohol dependence may reflect symptoms of central neuroadaptation or neurodegeneration, and successful treatment of alcoholism should reverse these changes and improve sleep persistently. For example, long-lasting alterations in GABAergic, adenosinergic, glutamatergic, dopaminergic and serotonergic neurotransmitter function have been implicated in withdrawal symptoms and relapse in alcohol-dependent patients and in animal models of alcohol dependence.[91-98] Treatment to normalise these neuro-

transmitter systems may be expected to improve sleep in the long term and prevent relapse in recovering patients.

In the US, the aldehyde dehydrogenase-blocker disulfiram and the opioid receptor antagonist naltrexone are the only medications approved by the Food and Drug Administration (FDA) to treat alcohol dependence. In Europe, acamprosate, an amino acid derivative that may normalise glutamatergic and GABAergic neurotransmission, is also in clinical use.[99,100] Whereas a small reduction of REM sleep was observed in an early study with disulfiram,[101] the effects of the other 2 agents on sleep in abstinent patients are unknown.

Unfortunately, only a few pharmacological and nonpharmacological strategies to improve sleep in individuals recovering from alcoholism have been studied. They are discussed in the sections 4.1 and 4.2.

4.1 Pharmacological Treatment

4.1.1 GABAergic Agents

BDZs have documented efficacy in the prevention or treatment of acute withdrawal symptoms such as seizures and DTs.[9,102] They are, however, not recommended for the treatment of alcohol-related sleep disturbances. They are cross-tolerant with alcohol and carry the risk of misuse or abuse themselves.[90] An early study showed that during 6 days after alcohol withdrawal using the BDZs chlordiazepoxide, REM sleep was initially suppressed, while SWS remained virtually eliminated.[38] A prominent reduction of EEG delta activity in non–REM sleep is a consistent finding with BDZs and analogues in healthy individuals, even after sleep deprivation.[103]

In alcohol-dependent rats, the GABA agonists muscimol and homotaurine reduced wakefulness and increased non–REM and REM sleep in the light period during the first day of alcohol withdrawal.[104] These effects were in contrast to those in animals that were not alcohol-dependent, in which no changes were seen. Whether the tonic stimulation of GABAergic neurotransmission can improve disturbed sleep in abstinent patients remains to be established.

Activation of $GABA_A$ receptors with THIP and presynaptic $GABA_B$ receptors with GHB[105] promotes SWS and SWA in young healthy men.[68,86] However, the low therapeutic index and considerable abuse potential of GHB[106] may limit the clinical potential of this agent in the treatment of alcohol dependence.

Preliminary findings indicate that gabapentin, which may increase the concentration of GABA in the brain, may improve subjective sleep quality during early abstinence in alcohol-dependent patients.[107]

4.1.2 Serotonergic Agents

It is well established that the 5-HT_2 receptor antagonists ritanserin and seganserin increase the amount of SWS and enhance EEG SWA in healthy humans and animals.[71,87,108,109] In contrast, ritanserin failed to promote SWS during 4 weeks of abstinence in 10 patients with chronic alcoholism and dysthymia who had undergone BDZ treatment until 7 days prior to the study compared with 10 patients in the placebo group.[110] Nevertheless, total sleep time, the duration of non–REM sleep and sleep efficiency were enhanced, wakefulness reduced, and symptoms of depression and anxiety improved when compared with placebo. Moreover, a preliminary clinical study suggested that ritanserin may reduce alcohol craving and the rate of relapses in 5 recently abstinent alcohol-dependent individuals.[111] In a large multicentre trial, however, no enhanced benefit of this drug was found when it was used as an adjunctive medication to cognitive-behavioural therapy in 423 patients.[112]

Based on clinical observations in healthy individuals and those who abuse alcohol, 5-HT_3 antagonists have been suggested to hold promise for the treatment of alcohol dependence.[99,113] Compared with other serotonin receptor subclasses, 5-HT_3 receptors appear to play a minor role in sleep-wake regulation.[114,115] In accordance with this view, only slight and nonconsistent changes in sleep variables and nocturnal endocrine measures were found in 8 healthy men during 5 days of tropisetron

administration.[116] However, a recent study including a total of 321 patients (160 patients with late onset alcoholism and 161 patients with early onset alcoholism) has indicated that distinct subgroups of alcohol-dependent patients may respond differently to 5-HT_3 receptor inhibition. Specifically, the selective antagonist ondansetron improved drinking and abstinence compared with placebo in the patients with early onset alcoholism (who developed the disorder at age ≤25 years), whereas it was not superior to placebo in the patients with late onset alcoholism (>25 years).[117] Whether the treatment affected sleep and whether the sleep effects differed between the diagnostic subgroups is unknown. Nevertheless, in view of a genetic heterogeneity between early and late onset alcoholism,[118] this study highlights the importance of pharmacogenetic approaches in the treatment of alcohol dependence.

4.1.3 Other Medications

Melatonin

Alcohol inhibits nocturnal synthesis of melatonin,[119] and night-time serum levels of the pineal hormone may be reduced in alcohol-dependent patients during withdrawal.[120] Preliminary studies of controlled release melatonin administered to improve sleep quality in patients with major depression and schizophrenia revealed equivocal results and did not report sleep EEG data.[121,122] Whether exogenous melatonin can ameliorate sleep objectively and/or subjectively during alcohol recovery has not been studied.

Ethanol

It may be reasonable to assume that controlled low dose administration of ethanol may prevent withdrawal symptoms. Two recent articles, however, disagree on the usefulness of this approach in the pharmacological management of alcohol withdrawal.[9,10] In one early study, SWS improved to normal levels within 3 to 4 days after ≈4 days of alcohol withdrawal moderated with a decreasing low dose of ethanol.[38] In contrast, SWS remained virtually absent during 6 days after ethanol withdrawal supported with the BDZ chlordiazepoxide. In another study, patients with low values of SWS after 2 to 3 weeks of abstinence (i.e. baseline) showed a larger SWS promotion with ethanol, yet a more rapid development of tolerance and a poorer treatment outcome after 2 months than patients with higher amounts of SWS at baseline.[38]

To our knowledge, these preliminary findings on the relationship between SWS and treatment outcome have not been replicated, and the efficacy and safety of low dose ethanol detoxification has not been evaluated in controlled clinical trials.

Antidepressants

Sedating antidepressants such as trazodone are commonly used during alcohol withdrawal, but their efficacy and safety have not been studied appropriately. Furthermore, selective serotonin reuptake inhibitors appear to be rather unsuitable as sleeping aids, and they have not been convincing in prevention of relapse in recovering alcohol-dependent patients.[99,100]

Treatments for Sleep Apnoea and Periodic Limb Movements

The connection between sleep disturbances and alcoholic relapse suggests that patients should be screened for the presence of sleep apnoea and periodic leg movements. The clinical treatment of these disorders has recently been reviewed elsewhere.[1,123-126]

4.2 Nonpharmacological and Alternative Treatments

Effective nonpharmacological strategies for the treatment of insomnia include:

- relaxation techniques
- cognitive therapy
- stimulus control methods
- sleep restriction
- sleep hygiene education (i.e. avoidance of caffeinated beverages near bedtime, adherence to regular sleep-wake habits, exercising during the day).[127,128]

Although the benefits of these methods have not been studied specifically for alcohol-related sleep disturbances, they can and should be included in

any intervention to treat insomnia in alcohol-dependent patients.

The results of pilot studies in small samples of recovering alcohol-dependent individuals on the effects of bright light therapy,[129] dawn simulation[130] and homeopathy[131] warrant further investigation. Larger controlled studies are needed involving longer treatment and observation periods, follow-up assessment and outcome evaluations, and providing standard polysomnographic data to allow guidelines for therapeutic interventions to be designed.

5. Conclusions

Alcohol has a negative impact on sleep. Even after moderate drinking in individuals who are not alcohol-dependent, sleep in the second half of the night may be interrupted by frequent awakenings and perceived as superficial and shallow due to increased dreaming, sweating and headache. These effects may occur even when no alcohol has been detected in breath or plasma at bedtime. Moreover, the substance may induce, or exacerbate, sleep apnoea and nocturnal myoclonus.

Virtually every type of sleep problem occurs in alcohol-dependent patients. They typically have a long sleep latency, low sleep efficiency, short sleep duration and reduced amounts of SWS. Their sleep patterns are fragmented, and sleep architecture is severely disrupted. The percentage of REM sleep may be reduced or increased. Subjective sleep disturbances may contribute to continued drinking, and persistent alterations of sleep during withdrawal and abstinence may increase the risk of relapse into alcoholism.

There remain many open questions regarding the mechanisms of action of short and long term alcohol use on sleep and the sleep EEG, and the relationship between sleep, sleep abnormalities and alcoholism. For example, what adaptive changes underlie the initial promotion of SWS and SWA, which is followed by impaired sleep consolidation after short term alcohol consumption? How do zero or near-zero amounts of alcohol in the plasma affect sleep and the sleep EEG? What mechanisms lead to suppression of SWS and disruption of normal non–REM/REM sleep cycles during long term alcohol ingestion? Can promotion of SWS and improvement of objective and subjective sleep quality prevent relapse into alcoholism? Are the sleep changes, which predict early relapse in alcohol-dependent patients, *per se* responsible for the poor therapeutic outcome, or do they reflect other underlying factors? Progress in the understanding of these and other questions[100] may lead to future therapies which improve sleep and reduce relapse in recovering patients.

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