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NEUROPSYCHOPHARMACOLOGY REVIEWS

Alcohol use disorder and sleep disturbances: a feed-forward allostatic framework

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The development of alcohol use disorder (AUD) involves binge or heavy drinking to high levels of intoxication that leads to compulsive intake, the loss of control in limiting intake, and a negative emotional state when alcohol is removed. This cascade of events occurs over an extended period within a three-stage cycle: *binge/intoxication*, *withdrawal/negative affect*, and *preoccupation/anticipation*. These three heuristic stages map onto the dysregulation of functional domains of incentive salience/habits, negative emotional states, and executive function, mediated by the basal ganglia, extended amygdala, and frontal cortex, respectively. Sleep disturbances, alterations of sleep architecture, and the development of insomnia are ubiquitous in AUD and also map onto the three stages of the addiction cycle. During the *binge/intoxication* stage, alcohol intoxication leads to a faster sleep onset, but sleep quality is poor relative to nights when no alcohol is consumed. The reduction of sleep onset latency and increase in wakefulness later in the night may be related to the acute effects of alcohol on GABAergic systems that are associated with sleep regulation and the effects on brain incentive salience systems, such as dopamine. During the *withdrawal/negative affect* stage, there is a decrease in slow-wave sleep and some limited recovery in REM sleep when individuals with AUD stop drinking. Limited recovery of sleep disturbances is seen in AUD within the first 30 days of abstinence. The effects of withdrawal on sleep may be related to the loss of alcohol as a positive allosteric modulator of $GABA_A$ receptors, a decrease in dopamine function, and the overactivation of stress neuromodulators, including hypocretin/orexin, norepinephrine, corticotropin-releasing factor, and cytokines. During the *preoccupation/anticipation* stage, individuals with AUD who are abstinent long-term present persistent sleep disturbances, including a longer latency to fall asleep, more time awake during the night, a decrease in slow-wave sleep, decreases in delta electroencephalogram power and evoked delta activity, and an increase in REM sleep. Glutamatergic system dysregulation that is observed in AUD is a likely substrate for some of these persistent sleep disturbances. Sleep pathology contributes to AUD pathology, and *vice versa*, possibly as a feed-forward drive to an unrecognized allostatic load that drives the addiction process.

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INTRODUCTION

Sleep is a ubiquitous complex behavior that is necessary to sustain mental and physical health in humans. The different states of sleep and transitions between sleep and wakefulness are supported by a complex set of patterns of neurological activation and neurotransmitter release [1]. Many of the neurotransmitters and brain systems that are known to be involved in sleep-wake regulation are also affected by alcohol (e.g., [2–4]). Thus, unsurprisingly, alcohol affects sleep in several ways. Acute intoxication can alter sleep, but the effects of alcohol show tolerance with repeated use and dependence [5, 6]. This tolerance is accompanied by adaptations of several neurotransmitter systems, either by modulating their release or modifying the sensitivity of their response mechanisms [7–10]. Withdrawal from alcohol in dependent individuals can be associated with neurological manifestations of a consequent neurochemical imbalance [5]. Over time, recovery can occur to restore a normal balance of inhibitory and excitatory systems, but some changes that are induced by alcohol may be resistant to restoration. The present review attempts to conceptually place the published literature that is relevant to the above factors into a three-stage cycle framework: *binge/intoxication*, *withdrawal/negative affect*, and *preoccupation/anticipation* ("craving").

Notably, several decisions were made with regard to which data are reviewed herein and the ways in which they are presented in the review. First, the salience of having sleep interrupted by periods of wakefulness is a potential driver of behavior. Therefore, the percentage of wakefulness after sleep onset (WASO%) is reported rather than the more typical inverse measure of sleep efficiency (i.e., the percentage of time in bed spent asleep). Second, wake and sleep stage data are reported as percentages of sleep time throughout the review. This is used rather than absolute time spent in each state because of differences between studies in amounts of time that are available for sleep, the age of the subjects, and other factors that can influence absolute time values. Third, wherever possible, data are presented as difference scores to normalize data across experiments. This helps address issues that are related to the fact that the studies that are reported herein were published over a period of more than four decades. Over this time, dramatic changes in recording technology have

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Glossary

	Definition	EEG characteristics
Wake	Clear evidence of conscious wakefulness.	alpha (8–12 Hz), beta (13–30 Hz), and gamma (>30 Hz)
N1	Waxing and waning of consciousness. Drowsiness.	alpha or beta alternating with theta (4–7 Hz)
N2	Clear sleep with the presence of sleep spindles and K-complexes.	theta and some delta (<4 Hz)
N3	Clear sleep, largely dominated by large slow voltage fluctuations.	prominent delta with some theta
REM	Rapid-eye-movement sleep with saccadic eye movements and lower muscle tone.	Mixture of beta and theta
NREM	Non-rapid-eye-movement sleep. Combination of stages N1, N2, and N3.	theta and delta
SWS	Slow-wave-sleep (now termed N3).	prominent delta with some theta
SWA	Slow wave activity, a measure of slow-frequency EEG power.	delta
Sleep spindle	Brief (0.5–1 s) bursts of oscillatory EEG.	sigma (12–16 Hz)
K-complex	Single high-amplitude EEG waveform with a duration of approximately 1 s.	delta

occurred, spanning the initial acceptance of consensus scoring rules for sleep stages [11] and gradual shifts in those rules and the ways in which they are applied [12]. If earlier papers tend to over- or underreport slow-wave sleep (SWS) or rapid-eye-movement (REM) sleep, then the values of interest are normalized to appropriate within-subject or between-group control data that should have the same issue. Finally, several papers in the past have highlighted REM latency or some measure of the intensity of eye movements in REM as distinguishing features of sleep in alcoholics [5]. Although these measures are indeed interesting, we have chosen to focus on the percentage of REM as a key measure in this review. This decision was based on the practical consideration that many more papers report REM% than the other measures.

The term Alcohol Use Disorder (AUD) is used throughout the manuscript, but this specific diagnosis is a relatively recent concept. Many of the studies that are cited herein used other diagnoses, such as "alcohol abuse" or "alcohol dependence" or even "alcoholism," based on various research or clinical definitions that were available at the time the research was conducted.

DIAGNOSTIC FEATURES: DEFINITIONS AND CONCEPTUAL FRAMEWORK OF ALCOHOL USE DISORDER

In AUD, a pattern of oral drug taking evolves that is often characterized by binges of alcohol intake that can be daily episodes or prolonged days of heavy drinking and is characterized by a severe emotional and somatic withdrawal syndrome. Many individuals with AUD continue with such a binge/withdrawal pattern for extended periods of time, but some individuals evolve into a situation in which they must have alcohol available at all times to avoid the negative consequences of abstinence. Here, intense preoccupation with obtaining alcohol (craving) develops that is linked not only to stimuli that are associated with obtaining the drug but also to stimuli that are associated with withdrawal and the aversive motivational state. A pattern ultimately develops in moderate to severe AUD in which the drug must be taken to avoid the severe dysphoria and discomfort of abstinence.

Alcohol use disorder can be defined as a chronically relapsing disorder that is characterized by a compulsion to seek and take the drug (alcohol), loss of control in limiting drug (alcohol) intake, and the emergence of a negative emotional state (e.g., dysphoria, anxiety, irritability, and hyperkatifeia), reflecting a motivational withdrawal syndrome, when access to the drug (alcohol) is prevented. These key elements incorporate most of the symptoms of AUD as expressed in moderate to severe AUD in the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5) [13].

The diagnostic criteria for AUD and addiction in general, as described in the DSM, have evolved from the first edition that was published in 1952 [14] to the current DSM-5 [13], with a shift from an emphasis on the criteria for tolerance and withdrawal to other criteria that are more directed toward compulsive use. In the DSM-5 [13], the new diagnostic criteria for addiction merged the abuse and dependence constructs (i.e., substance abuse and substance dependence) into one continuum that defines "alcohol use disorder" on a range of severity, from mild to moderate to severe, based on the number of criteria that are met out of 11 criteria.

Alcohol use disorder and addiction in general have been heuristically framed as a three-stage cycle: *binge/intoxication*, *withdrawal/negative affect*, and *preoccupation/anticipation* ("craving") [15] (Fig. 1). These three stages represent dysregulation in three functional domains (incentive salience/pathological habits, negative emotional states, and executive function, respectively). While formulated as a heuristic framework, a study that was designed to identify the domains that drive addiction based on a factor analysis of a deeply phenotyped clinical sample using a broad range of human testing scales and neuropsychological tests supported the existence of incentive salience, negative emotionality, and executive function as domains that are relevant to AUD [16, 17].

As originally described, the cycle of addiction was hypothesized to reflect a spiral of self-regulation pathology and increasing motivation for compulsive drug seeking [15]. Motivation that drives the initial drug seeking from positive reinforcement was argued to shift to an additional source of motivation that drives continued drug seeking from negative reinforcement [18]. Negative reinforcement can be defined as the process by which the removal of an aversive stimulus (e.g., negative emotional state of drug withdrawal) increases the probability of a response (e.g., dependence-induced drug intake to relieve the negative emotional state). Driving negative reinforcement is a negative emotional state that is a common presentation in most individuals with AUD during withdrawal and protracted abstinence. Importantly, negative reinforcement is not punishment, although both involve an aversive stimulus. In punishment, the aversive stimulus suppresses behavior, including drug taking (e.g., disulfiram [Antabuse]). Negative reinforcement can also be considered reinforcement via relief, such as by removal of the negative emotional state of acute withdrawal or protracted abstinence.

The three domains are hypothesized to be mediated by three major neurocircuitry elements (basal ganglia, extended amygdala, and prefrontal cortex, respectively) [19, 20] (Fig. 1). The three

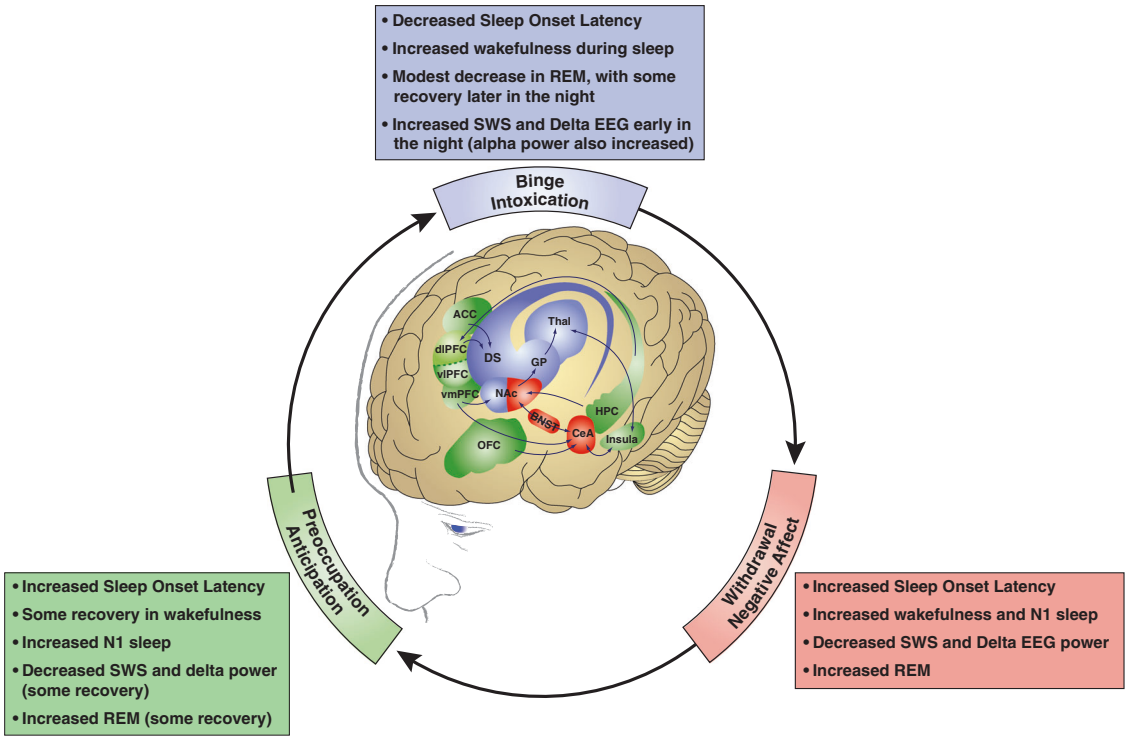

Fig. 1 Sleep dysregulation during alcohol addiction incorporated into the three-stage conceptual framework for the neurobiological basis of addiction. In the *binge/intoxication* stage, reinforcing effects of drugs may engage reward neurotransmitters and associative mechanisms in the nucleus accumbens shell and core and then engage stimulus-response habits that depend on the dorsal striatum. Two major neurotransmitters that mediate the rewarding effects of drugs of abuse are dopamine and opioid peptides. In the *withdrawal/negative affect* stage, the negative emotional state of withdrawal may engage activation of the extended amygdala. The extended amygdala is composed of several basal forebrain structures, including the bed nucleus of the stria terminalis, central nucleus of the amygdala, and possibly a transition zone in the medial portion (or shell) of the nucleus accumbens. Major neurotransmitters in the extended amygdala that are hypothesized to function in negative reinforcement are corticotropin-releasing factor, norepinephrine, and dynorphin. There are major projections from the extended amygdala to the hypothalamus and brainstem. The *preoccupation/anticipation* (craving) stage involves the processing of conditioned reinforcement in the basolateral amygdala and the processing of contextual information by the hippocampus. Executive control depends on the prefrontal cortex and includes the representation of contingencies, the representation of outcomes, and their value and subjective states (i.e., craving and, presumably, feelings) that are associated with drugs. The subjective effects, termed "drug craving" in humans, involve activation of the orbitofrontal and anterior cingulate cortices and temporal lobe, including the amygdala. A major neurotransmitter that is involved in the craving stage is glutamate that is localized in pathways from frontal regions and the basolateral amygdala that project to the ventral striatum. ACC, anterior cingulate cortex; BNST, bed nucleus of the stria terminalis; CeA, central nucleus of the amygdala; DS, dorsal striatum; dlPFC, dorsolateral prefrontal cortex; GP, globus pallidus; HPC, hippocampus; NAC, nucleus accumbens; OFC, orbitofrontal cortex; Thal, thalamus; vlPFC, ventrolateral prefrontal cortex; vmPFC, ventromedial prefrontal cortex. Modified from [19]

stages are conceptualized as interacting with each other, becoming more intense, and ultimately leading to the pathological state that is known as addiction [15].

Derived largely from fundamental work in neurobiology, the thesis argued herein is that AUD is a brain neurocircuitry disorder and that neuroadaptations within specific motivational circuits play an important role in defining and perpetuating the disorder. As formulated, the excessive engagement of reward circuitry engages high incentive salience for cues and contexts that are conditioned to drug seeking (*binge/intoxication* stage) and drives pathological habits. These functional changes in reward and habit circuits set up a series of neuroadaptations that involve core deficits of lower reward function and the greater activation of brain stress systems (*withdrawal/negative affect* stage) and significant impairment in executive function, all of which contribute to the compulsive drinking that is associated with AUD (Fig. 1).

For the *binge/intoxication* stage, several major neurotransmitter systems (e.g., γ-aminobutyric acid [GABA], glutamate, endogenous opioids, and dopamine) converge on the nucleus accumbens for the intoxicating and incentive salience effects of alcohol and glutamate and dopamine in the basal ganglia for the development of pathological habits [21].

In the neurocircuitry and neuropharmacology of the *withdrawal/negative affect* stage, the persistent increase in motivation that is associated with dependence in addiction [22, 23] is conceptualized as a cycle of the increasing dysregulation of brain reward/anti-reward mechanisms that results in a negative emotional state that contributes to the compulsive use of drugs. This negative emotional state in AUD has been hypothesized to be driven not only by the loss of reward function that is mediated by GABA, endogenous opioids, and dopamine but also by a gain in brain stress neurotransmitter system function (e.g., corticotropin-releasing factor [CRF], norepinephrine, hypocretin, and dynorphin) and neuroimmune function, all of which converge on parts of the extended amygdala, including elements of the nucleus accumbens) [20, 21]. There are also anti-stress, "buffer" neuromodulatory systems that also converge on the extended amygdala (e.g., neuropeptide Y [NPY], nociceptin, endocannabinoids, and oxytocin) that may be compromised during the development of alcohol addiction, also contributing to the malaise of acute and protracted withdrawal [20, 24].

The neurocircuitry that drives the *preoccupation/anticipation* or "craving" stage of the addiction cycle is hypothesized to mediate relapse in humans not only by the constructs of impulsivity and compulsivity but also by elements that define protracted

abstinence and craving. Human imaging studies have revealed neurocircuitry dysregulation during the *preoccupation/anticipation* stage in AUD that includes compromises in frontal cortical executive function and the dysregulation of substrates that mediate craving. Lower frontal cortex activity parallels deficits in executive function in neuropsychologically challenging tasks in AUD [25], and deficits in executive function (e.g., response disinhibition, expectations, and impulsivity) have been linked to craving in addiction [26]. Neurotransmitter systems that are involved in craving in animal models of cue-induced reinstatement have primarily focused on a glutamatergic projection from the frontal cortex and basolateral amygdala to the nucleus accumbens [27].

MAPPING THE NEUROSCIENCE MODEL OF ADDICTION ONTO SLEEP: ALCOHOL INTERACTIONS

Human sleep is defined on the basis of changes in electroencephalographic (EEG) activity, augmented by measurements of eye movements and postural muscle tone to aid in the differentiation of REM sleep from wakefulness. There is a continuum of predominant EEG frequencies from wakefulness through REM sleep to deep SWS. Wakefulness is associated with very high frequency gamma oscillations (≥~40 Hz) and desynchronized beta activity (~20–30 Hz). Relaxed wakefulness, especially when the eyes are closed prior to sleep, is associated with synchronized alpha oscillations (~10 Hz) that are predominant at occipital scalp sites. This gives way to slower, mixed-frequency theta activity (4–7 Hz) in stage 1, light non-REM (NREM) sleep (N1) [12], although N1 is characterized by drowsiness with the waxing and waning of consciousness that maps onto the waxing and waning of alpha (consciousness) and theta (unconscious) activity. REM sleep, constituting 20–25% of the night, exhibits desynchronized activity in the theta and beta ranges, reflecting the partial reactivation of brainstem mechanisms that are fully active in wakefulness and deactivated in NREM sleep. Stage 2 NREM sleep (N2) is characterized by theta activity, some delta activity (0.3–2 Hz), phasic sleep spindles (synchronized sigma activity: 12–16 Hz), and K-complexes (high-amplitude single delta waves) and constitutes between 45–55% of the night. Stage 3 and 4 NREM sleep (N3 or SWS) is characterized by slow delta activity that comprises ~18% of the night. NREM and REM sleep alternate across the night in ~90-min cycles. As the sleep episode progresses, Stage 2 sleep accounts for most NREM sleep, and the amount of REM sleep increases.

Acute effects of alcohol on sleep: binge/intoxication domain

Alcohol's sedative actions on the central nervous system (CNS) can lead to sleepiness and sleep. The impact of acute alcohol ingestion prior to sleep can be reasonably assumed to vary, based on a number of factors, including blood alcohol levels at sleep onset, the time of the last drink relative to sleep onset, the time taken to metabolize alcohol and eliminate it and its major metabolites, age, sex, and body fat percentage. The metabolism of alcohol by liver enzymes is unaffected by sleep [28]. Thus, over the duration of an extended period of sleep, blood levels of alcohol and major metabolites (e.g., acetaldehyde and acetate) vary substantially and are expected to impact sleep differently at different points in the sleep cycle. Given the pharmacokinetics of alcohol absorption, blood alcohol levels may continue to rise during sleep if alcohol is consumed immediately prior to sleep onset but will eventually fall after metabolism and elimination, according to the pharmacokinetics that are provided by the status of liver function and genetic factors in the production of liver enzymes [29]. In addition to the direct effect of alcohol and metabolites on sleep and possible early withdrawal opponent processes, it is also necessary to consider more prosaic secondary effects, such as diuresis, on sleep disturbances.

A key interrelationship between alcohol intoxication and sleep is its potential to generate erroneous beliefs about alcohol as an effective self-administered therapy for insomnia [30, 31]. There is, however, only a small body of literature that reports laboratory investigations of the ways in which acute intoxication impacts sleep. Results have varied between studies because of typical sources of variance in human physiology experiments, such as small sample sizes, the lack of consistency in dosing schedules and amounts, and the gender and age distributions of the subject populations.

Acute effects of alcohol on sleep: time to fall asleep and wakefulness after sleep onset

Sleep is a rapidly reversible unconscious state. However, beliefs about how substances or behaviors influence sleep quality are based on conscious experience, either how a person feels the next day (e.g., sleepy/rested, good/bad mood, etc.) or their remembered experience of wakeful consciousness around the sleep period (e.g., time taken to fall asleep, time spent awake during the night, etc.). Thus, such measures as sleep onset latency, time spent awake after sleep onset, and sleep efficiency (time asleep/time in bed) based on the perception that alcohol accelerates sleep onset are more salient in terms of developing and reinforcing beliefs than measures of REM sleep or SWS or how much delta EEG power is generated during the sleep period. Several studies have used non-intoxicating doses of alcohol. Reviews of these data can be found in Colrain et al. [5] and Ebrahim et al. [6].

Table 1 summarizes sleep onset latency (SOL) data, typically measured as the time from lights out to the onset of stage 1 (N1) sleep, taken from studies that either had a single night of alcohol administration, or in the first night of several nights [28, 32–42]. The average SOL for the no-dose nights in studies of rested, healthy controls was around 15 min across studies. Intoxicating doses of alcohol appear to lead to a modest reduction of SOL by ~5 min at doses ≥0.9 g/kg. Although this effect may seem small, even zolpidem (i.e., arguably the current gold standard pharmacological treatment for insomnia) sometimes shows effects of similar magnitude when administered to healthy controls [43, 44].

Another sleep variable with high salience is the number of minutes spent awake after sleep onset (WASO). Table 2 shows WASO data from a number of studies that split the night into early and later periods [28, 32, 33, 38, 39, 41, 42] to separate high blood alcohol levels early in the night from falling blood alcohol levels, but also possibly still high metabolite levels later in the night. Data from whole night studies show a small increase in WASO with high alcohol doses. Data from split night studies show a tendency toward a decrease in WASO in the first half of the night following intoxicating doses of alcohol but an increase in the second half of the night, with a similar effect magnitude regardless of the intoxicating dose that is administered. Other sleep continuity variables, such as the number of awakenings and sleep efficiency (i.e., minutes asleep as a proportion of time in bed), show similar trends [39, 42]. Supplementary Table S1 shows data from studies that reported across the entire night [32, 34–40, 45]. Notably, in two studies, Roehrs and colleagues showed *increases* in WASO with alcohol in insomnia patients [37] and in controls who had restricted sleep on the prior night [36]. Thus, even in cases in which prior sleep is poor, the net effect of an intoxicating alcohol dose is to *worsen* sleep by increasing WASO.

There is one other study worth noting [46] that differs from those reviewed above, in which alcohol was consumed in the afternoon, 6 h before bedtime. The 0.55 g/kg dose of vodka that was administered to subjects led to an initial breath alcohol level of 0.08 g%, which decreased to zero before sleep onset. No difference in sleep onset latency was found between control and alcohol nights, but WASO substantially increased on alcohol nights (66.9 *vs*. 38.7 min), and the effect was maximal later in the night. The data confirm the general trend of the other studies, in which

Table 1. Sleep onset latency (minutes) in studies that compared a no-dose (placebo or no alcohol) night to nights in which different doses of alcohol were administered prior to bed

Studies of controls	*n*/Sex	No dose	0.50–0.64 g/kg	0.75–0.80 g/kg	0.90–1.20 g/kg
Rundell et al. [28]	10 M	**15.7**			−5.0
Stone [32]	6 M	**18.0**	−4.8		
MacLean and Cairns [33]	10 M	**28.0**	−16.0	−16.0	−13.2
Scrima et al. [34] (controls)	4 M, 2 F	**1.0**		5.0	
Williams et al. [35]	11 F	**24.2**	−10.2	−11.8	
Roehrs et al. [36] (8 h tib previous night)	5 M	**14.4**		+7.6	
Roehrs et al. [37] (controls)	9 M+F	**11.9**	−1.8		
Van Reen et al. [38]	7 F	**4.0**	+1.0		
Feige et al. [39]	5 M, 5 F	**16.9**			−6.6
Arnedt et al. [40] (male subjects)	34 M	**12.9**			−3.9
Arnedt et al. [40] (female subjects)	59 F	**8.6**			+0.1
Sagawa et al. [41]	10 M	**6.9**	−3.1		−4.2
Chan et al. [42]	12 M, 12 F	**16.9**		−2.7	
Median values for studies of controls		**14.8**	**−4.0**	**−2.7**	**−4.6**
Studies of non-normal sleep					
Scrima et al. [34] (OSA)	5 M			−6.0	
Roehrs et al. [36] (4 h tib previous night)	5 M	**11.0**		+5.1	
Roehrs et al. [37] (insomniacs)	11 M+F	**9.9**	+4.7		

Doses were collapsed into ranges of 0.25–0.32, 0.40–0.75, and 0.90–1.20 g/kg to facilitate comparison. The bold data in the "No dose" column reflect the values seen when alcohol was not administered. The data in each dose column reflect differences between the dose that was administered and the corresponding "No dose" condition. Positive values indicate an increase relative to "No dose," and negative values indicate a decrease. The median values across studies of normal controls are presented as data from subjects with abnormal sleep (e.g., sleep restriction on the previous night or a diagnosis of a sleep disorder). M = male subjects. F = female subjects. M+F indicates that the gender distribution was not provided in the paper

the effects on SOL are probably attributable to alcohol, and the effects on WASO are attributable to neuroadaptations to alcohol or the presence of alcohol metabolites.

In summary, the acute effects of alcohol on the time taken to fall asleep are highly variable, even at high alcohol doses. The amount of time spent awake during the sleep period tends to decrease early in the night and then increase later in the night when high doses of alcohol are administered prior to bed, leading to an overall increase across the night. Therefore, somewhat paradoxically, despite alcohol's sedative effects and the strongly held societal beliefs about its efficacy as a sleep aid, although the time taken to fall asleep decreases modestly, the amount of time spent awake during the night increases following the consumption of intoxicating levels of alcohol prior to bedtime.

Binge/intoxication: effects on REM sleep

The consensus view in the literature is that alcohol suppresses REM sleep, with a rebound increase in REM sleep that occurs when blood alcohol levels decrease. For the first half of the night (Table 3), relative to the no-alcohol condition, studies that administered 0.50–0.64 g/kg alcohol reported a median 0.7% increase in REM as a percentage of sleep time. Studies that administered 0.75–0.80 g/kg alcohol reported a median 6.7% decrease, and studies that administered 0.90–1.2 g/kg alcohol reported a median 2.6% decrease. There is some evidence of rebound in the second half of the night, other than when the highest doses of alcohol were used. In the second half of the night, relative to the no-alcohol condition, studies that administered 0.50–0.64 g/kg alcohol reported a median 5% increase in REM as a percentage of sleep time. Studies that administered 0.75–0.80 g/kg alcohol reported a median 6.5% increase, but studies that administered 0.90–1.2 g/kg alcohol reported a median 2.1% decrease. Intoxicating doses of alcohol, however, show variable results when data are collapsed over the entire night (Supplementary Table S2). The percentage of REM sleep across the entire night in studies of normal controls ranged from 17.3% to 24.2%, with a median of 23.1% on no-dose nights. Relative to the no-dose condition, studies that administered 0.50–0.64 g/kg alcohol reported a median 0.7% decrease in REM sleep as a percentage of sleep time. Studies that administered 0.75–0.80 g/kg alcohol reported a median 3.5% decrease, and studies that administered 0.90–1.2 g/kg alcohol reported a median 2.9% decrease.

The general conclusion is that intoxicating doses of alcohol do not suppress REM sleep; instead, they produce a modest decrease that is most prominent early in the night, with some modest rebound compensation later in the night. Thus, the effects on REM sleep are likely mediated by alcohol itself rather than its metabolites. However, there was a trend in the Landolt et al. study [46] toward a decrease in REM sleep following afternoon alcohol administration (17.4% *vs.* 19.2% of total sleep time [TST], despite breath alcohol levels of zero at sleep onset.

Binge/intoxication: effects on NREM sleep

The major focus of studies that have examined NREM sleep has been on evaluating the effect of alcohol intoxication on light stage 1 drowsiness (N1) as a marker of poor sleep and SWS (N3) as a marker of restorative sleep. Data from studies that reported N1 sleep across the night are presented in Table 4. The median for the no-dose condition in healthy controls is ~7 min. Relative to the no-dose condition, all doses led to median effects of less than a 2% increase in N1 across the night. Consistent with the data on WASO, N1 following alcohol intoxication was slightly lower in the first half of the night relative to no-dose nights and slightly higher in the second half of the night (Supplementary Table S3).

The consensus view in the literature is that alcohol increases SWS, particularly early in the night when it typically

Table 2. Wakefulness after sleep onset (WASO; % of total sleep time [TST]) in studies that compared a no-dose (placebo or no alcohol) night to nights in which different doses of alcohol were administered prior to bed and in which data were separated into different portions of the night

Split night studies	Portion of night	*n*/Sex	No dose	0.50–0.64 g/kg	0.75–0.80 g/kg	0.9–1.20 g/kg
Rundell et al. [28]	1st half	10 M	**7.6**			−2.1
	2nd half		**4.2**			+0.5
Prinz et al. [45]	1st half	5 M	**8.7**		+1.7	
MacLean and Cairns [33]	1st 3 h	10 M	**12.9**	−8.3	−7.5	−9.7
	Hour 5		**0.6**	−0.1	+6.9	+17.2
Van Reen et al. [38]	1st 4 h	7 F	**12.0**	−3.0		
	2nd 4 h		**11.0**	+1.0		
Feige et al. [39]	1st half	5 M, 5 F	**8.5**			−3.5
	2nd half		**12.8**			+6.3
Sagawa et al. [41]	1st 3 h	10 M	**6.1**	−3.8		−5.2
Chan et al. [42]	1st half	12 M, 12	**8.5**		−0.3	
	2nd half		**25.1**		+13.3	
Median values for first half			**8.5**	−3.8	−0.3	−4.3
Median values for second half			**11.0**	+0.5	+10.1	+6.3

Doses were collapsed into ranges of 0.25–0.32, 0.40–0.75, and 0.90–1.20 g/kg to facilitate comparison. The bold data in the "No dose" column reflect the values seen when alcohol was not administered. The data in each dose column reflect differences between the dose that was administered and the corresponding "No dose" condition. Positive values indicate an increase relative to "No dose," and negative values indicate a decrease. The median values across studies of normal controls are presented separately for data that were collected early and those collected later in the night, typically the first and second halves of the recordings. M = male subjects. F = female subjects

Table 3. REM sleep in studies that compared a no-dose (placebo or no alcohol) night to nights in which different doses of alcohol were administered prior to bed and in which data were separated into different portions of the night

Split night studies	Portion of night	n/Sex	No dose	0.50–0.64 g/kg	0.75–0.80 g/kg	0.9–1.2 g/kg
Rundell et al. [28]	1st half	10 M	**12.7%**			−3.0%
	2nd half		**30.3%**			+8.6%
Prinz et al. [45]	1st half	5 M	**17.3%**		−9.4%	
MacLean and Cairns [33]	1st 3 h	10 M	**11%**	+0.7%	−0.4%	−2.0%
	Hour 5		**18%**	+14.5%	+14.2%	−8.5%
Van Reen et al. [38]	1st 4 h	7 F	**12.9%**	+1.7%		
	2nd 4 h		**32.1%**	−4.6%		
Feige et al. [39]	1st half	5 M, 5 F	**14.3%**			−2.6%
	2nd half		**24.5%**			+0.4%
Sagawa et al. [41]	1st 3 h	10 M	**8.6%**	+0.3%		−5.4%
Arnedt et al. [40] (all subjects)	1st half	34 M, 59 F	**23.0%**			+0.6%
	2nd half		**27.3%**			−4.7%
Chan et al. [42]	1st half	12 M, 12 F	**13.3%**		−6.7%	
	2nd half		**28.2%**		−1.1%	
Median values for first half			**13.1%**	+0.7%	−6.7%	−2.6%
Median values for second half			**27.8%**	+5.0%	+6.5%	−2.1%

Doses were collapsed into ranges of 0.25–0.32, 0.40–0.75, and 0.90–1.20 g/kg to facilitate comparison. The bold data in the "No dose" column reflect the values seen when alcohol was not administered. The data in each dose column reflect differences between the dose that was administered and the corresponding "No dose" condition. Positive values indicate an increase relative to "No dose," and negative values indicate a decrease. The median values across studies of normal controls are presented separately for data that were collected early and those collected later in the night, typically the first and second halves of the recordings. M = male subjects. F = female subjects

predominates. As seen in Supplementary Table S4, the studies showed a range of SWS in the no-dose condition between 12% and 30.5% of TST across the whole night. When collapsing the data across the whole night of sleep, a modest dose-related increase in SWS was observed. As shown in Table 5, however, this effect was highly variable across the night. There were increases in SWS following intoxication relative to the no-dose condition in the first half of the night, followed by decreases in the second half of the night when WASO and N1 increased.

The general conclusion for NREM sleep is that intoxicating doses of alcohol lead to increases in SWS early in the night but a deterioration of sleep quality (i.e., an increase in N1 and decrease in SWS later in the night).

Table 4. Stage 1 sleep (%total sleep time [TST]) in studies that compared a no-dose (placebo or no alcohol) night to nights in which different doses of alcohol were administered prior to bed

Studies of controls	*n*/Sex	No dose	0.50–0.64 g/kg	0.75–0.80 g/kg	0.9–1.20 g/kg
Stone [32]	6 M	**8.7%**	1.3%		
Williams et al. [35]	11 F	**3.9%**	+2.4%	+5.3%	
Roehrs et al. [36] (8 h tib previous night)	5 M	**11.9%**		−1.9%	
Roehrs et al. [37] (controls)	9 M+F	**12.3%**	−0.5%		
Van Reen et al. [38]	7 F	**9.0%**	+0.6%		
Feige et al. [39] (0.10% blood alcohol level condition)	5 M, 5 F	**5.2%**			+1.2%
Arnedt et al. [40] (male subjects)	34 M. 59 F	**4.5%**			−0.4%
Arnedt et al. [40] (female subjects)		**3.5%**			+0.5%
Median values for studies of controls		**6.9%**	+1.0%	+1.7%	+0.5%
Studies of non-normal sleep					
Roehrs et al. [36] (4 h tib previous night)	5 M	**9.4%**		−2.3%	
Roehrs et al. [37] (insomniacs)	11 M+F	**15.7%**	+0.5%		

Doses were collapsed into ranges of 0.25–0.32, 0.40–0.75, and 0.90–1.20 g/kg to facilitate comparison. The bold data in the "No dose" column reflect the values seen when alcohol was not administered. The data in each dose column reflect differences between the dose that was administered and the corresponding "No dose" condition. Positive values indicate an increase relative to "No dose," and negative values indicate a decrease. The median values across studies of normal controls are presented as data from subjects with abnormal sleep (e.g., sleep restriction on the previous night or a diagnosis of a sleep disorder). M = male subjects. F = female subjects. M+F indicates that the gender distribution was not provided in the paper

Table 5. Slow-wave sleep in studies that compared a no-dose (placebo or no alcohol) night to nights in which different doses of alcohol were administered prior to bed and in which data were separated into different portions of the night

Split night studies	Portion of night	*n*/Sex	No dose	0.50-0.64 g/kg	0.75-0.80 g/kg	0.9-1.20 g/kg
Rundell et al. [28]	1st half	10 M	**29.9%**			+3.4%
	2nd half		**6.9%**			-4.6%
Prinz et al. [45]	1st half	5 M	**30.5%**		+8.2%	
MacLean and Cairns [33]	1st 3 h	10 M	**39.1%**	+0%	+4%	+7%+
	Hour 5		**13.8%**	-6%	-9%	-9%
Van Reen et al. [38]	1st 4 h	7 F	**35.0%**	+0.4%		
	2nd 4 h		**9.6%**	+0.0%		
Williams et al. [35]	Hours 1–3	11 F	**24.8%**	+4%	+6%	
	Hours 4–6		**7.0%**	-3%	-6%	
Feige et al. [39]	1st half	5 M, 5 F	**20.0%**			+11.0%
	2nd half		**4.1%**	+0.0		−2.1%
Sagawa et al. [41]	1st 3 h	10 M	**27.0%**	+2.1%		+5.5%
Arnedt et al. [40] (all subjects)	1st half	34 M, 59 F	**25.3%**			
	2nd half		**27.3%**			+1.1%
Chan et al. [42]	1st half	12 M, 12 F	**44.0%**		+5.2%	−4.7%
	2nd half		**12.1%**		-5.6%	
Median values for first half			**29.9%**	+1.3%	+5.2%	+5.5%
Median values for second half			**9.6%**	-3.5%	-5.6%	−3.4%

Doses were collapsed into ranges of 0.25–0.32, 0.40–0.75, and 0.90–1.20 g/kg to facilitate comparison. The bold data in the "No dose" column reflect the values seen when alcohol was not administered. The data in each dose column reflect differences between the dose that was administered and the corresponding "No dose" condition. Positive values indicate an increase relative to "No dose," and negative values indicate a decrease. The median values across studies of normal controls are presented separately for data that were collected early and those collected later in the night, typically the first and second halves of the recordings. M = male subjects. F = female subjects

Binge/intoxication: effects on EEG

The impact of alcohol on the sleep architecture measures that are reported above are based on visual analysis of polysomnogram (PSG) recordings that are based on a consensus scoring system of pen chart recorder data that were adopted in 1968 [11] that was itself based on work from the 1930s [47–49]. Digital recordings have now replaced analog ink-on-paper records, and digital signal processing of the EEG can reveal subtle effects of alcohol that may vary according to brain region and that are not evident from the manual scoring of PSGs.

Few investigations have examined the acute effects of alcohol on EEG power spectra, the results of which are summarized in Table 6. The interpretation of the data is complicated by a number of factors. Rundell et al. [28] reported data only from a single

Table 6. Studies that used spectral analysis of sleep EEG following alcohol administration prior to bedtime

Studies of controls	*n*/Sex	Portion of night	Dose	Delta	Theta	Sigma	Alpha	Beta
Rundell et al. [28]	10M	Whole night	0.9 g/kg	No change			Increase[a]	Decrease[b]
		1st half			Decrease		Increase[a]	Decrease[b]
Dijk et al. [50]	8M	Hours 1-2	0.6 g/kg	Increase[d]				Decrease[d]
		Whole night			Decrease[e]			
Landolt et al. [46]	10M	Whole night[f]	0.55 g/kg	Increase[d]				
Van Reen et al. [38]	7 F	Whole night	0.49 g/kg		Increase[c, d]		Increase[d]	Increase[e]
		1st two sleep cycles					Increase[d]	
Chan et al. [51]	12M, 12 F	Cycle 1	~0.8 g/kg	Increase[d]			Increase[d]	
		Cycle 2					Increase[d]	
		Cycle 3					Increase[d]	
		Cycle 4		Decrease[d]			Decrease[d]	

Commonly used frequency bands are marked as significantly increased or decreased relative to a no-dose condition
[a]Increase was in the 1st derivative
[b]Significant at F3 but not C3
[c]4 Hz only
[d]In NREM
[e]In REM
[f]Alcohol administered 5 h prior to bedtime with blood alcohol level of 0.0 at lights out. M = male subjects. F = female subjects

central EEG site for delta, theta, and alpha activity and from a frontal site for higher frequencies. Dijk et al. [50] reported data only from a single central electrode. Landolt et al. [46] reported data from several scalp regions and showed frontal and central EEG effects but only in the first sleep cycle and in response to alcohol that was administered 6 h prior to sleep.

The frontal predominance was supported by Van Reen et al. [38] in a study of young women who ingested alcohol in the hour prior to sleep, with an increase in NREM alpha that lasted all night, but the increase in NREM delta was specific to the first sleep cycle. Chan et al. [51] confirmed the alpha and delta EEG effects, in which both frequencies had larger effects over the frontal scalp and showed a decrease in the magnitude of both across sleep cycles.

Similar to SWS, delta power increases early in the night and can decrease later in the night following intoxication. Thus, for the low-frequency EEG that is dominant in SWS, the frequency analysis is consistent with visual scoring. Alpha activity that is typically seen in relaxed wakefulness does not track WASO. Alpha increases in the first half of the night. Chan et al. [51] reported that it can occur in the context of background delta activity as so-called alpha-delta sleep. This pattern, which has been seen in patients with pain or who awake unrefreshed [52], could indicate that despite increases in delta activity and SWS, sleep may be less restorative following alcohol intoxication.

Binge/intoxication: repeated administration over several nights

If a relationship exists between the development of AUD and sleep issues that are associated with intoxication, then such a relationship emerges over the course of multiple days of drinking and may not be reflected by data from a single-night study. Unfortunately, only very few studies have assessed effects of the repeated administration of intoxicating doses of alcohol on sleep over several nights. In studies that investigated SOL over multiple nights of alcohol administration [28, 39], SOL was reduced across all three drinking nights [28, 39], with no clear evidence of adaptation of the effect over the three consecutive nights. The effects of a decrease in WASO in the first half of the night showed little change over three nights in two studies [28, 39] but showed evidence of *increases* over nine nights in another study [45]. WASO in the second half of the night was elevated relative to baseline across all drinking nights when all drinking nights were assessed [28, 39] (not reported in [45]).

For REM sleep, neither Rundell et al. [28] nor Feige et al. [39] reported systematic effects over the three nights for either the first or the second half of the night (Fig. 2). Prinz et al. [45] reported a decrease on night 1 that was still present on night 9 for the first half of the night but did not present data for the second half. For SWS, both Rundell et al. [28] and Feige et al. [39] reported initial increases for the first half of the night that appeared to habituate over the three nights of the study. For the second half of the night, both studies reported decreases in SWS that stayed flat over the three nights (Fig. 2). Prinz et al. [45] reported an initial increase that was not seen on night 9.

Drawing definitive conclusions from these three studies is difficult. In terms of WASO, however, drinking over multiple days does not appear to lead to habituation of the effects that are seen in studies of a single night of sleep following intoxication.

Binge/intoxication: sleep effects of alcohol administration in AUD

Experimental studies of the impact of alcohol intoxication on sleep in healthy controls are useful for providing insights into the ways in which intoxication might impact sleep and the ways in which the effects on sleep might contribute to the development of AUD. However, a clearer understanding of this relationship might be produced by studying the impact of alcohol intoxication on sleep in AUD patients. Such studies are not currently possible because of ethical and treatment guidelines for AUD. In the early 1970s, however, a few studies were conducted that are useful for review. These studies were conducted not long after the development of consensus standards for sleep scoring [11] with equipment that had recording and analysis limitations relative to equipment that is available to investigators today. Thus, some caution needs to be exercised when looking at absolute values of the data, but relative changes within datasets can still be informative.

Johnson et al. [53] studied 14 alcoholics for two nights following days in which they consumed bourbon every 2 h starting at 0800 hours. All of the subjects had a blood alcohol level of at least 0.11 g% at 8:00 PM. SOL did not change substantially in recovery *vs*. drinking. WASO and N1 (20% and 22%, respectively) appeared to be slightly higher when drinking compared with the first (18% and 15%) and last (17% and 18%) recovery nights. SWS decreased from a very low 3.2–2.1% on the first recovery night but

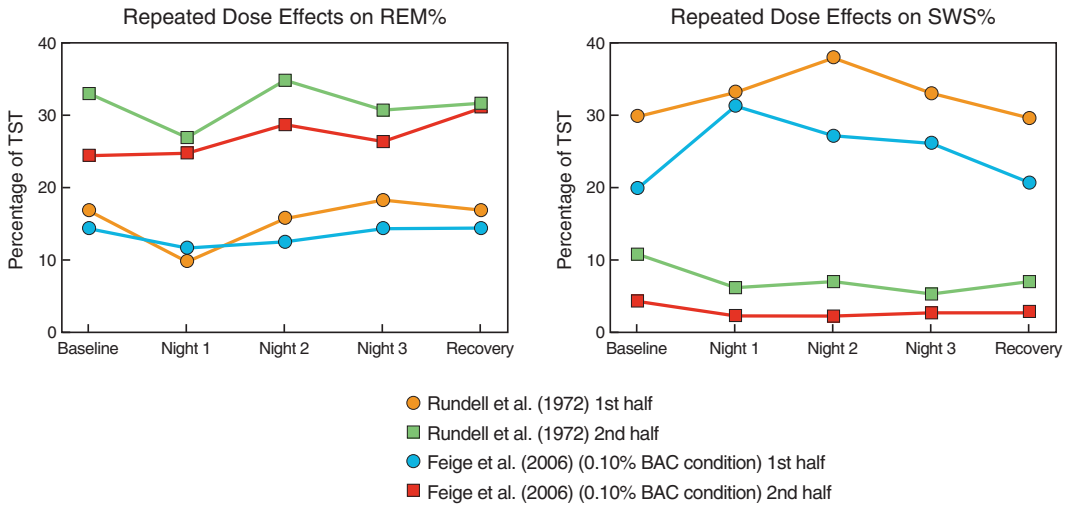

Fig. 2 Data from Rundell et al. [28] and Feige et al. [39]. REM% (left panel) and SWS% (right panel) in healthy controls sober at baseline, from three nights of drinking and the first recovery night. Data are presented separately for the first and second halves of the night

progressively increased to 5.8% by the last recovery night. REM sleep increased from 18% when drinking to 21% on the first recovery night and showed no further changes (Supplementary Table S5).

Allen et al. [54] reported data from six male alcoholics, five of whom were studied for 3–7 days while drinking 30 ml of 95% pure alcohol in juice every 2 h from 0800 to 2200 hours. All of the subjects were then denied alcohol and studied for the first 7 days of abstinence. Data were then collected after a further week of abstinence. The sixth subject was withdrawn from alcohol on admission and studied for 1 week of withdrawal and then after a further week of abstinence. For the present review, data are summarized by averaging all of the drinking nights and comparing them to nights off alcohol for the first five subjects. Because of technical issues, filtering of the data for several subjects did not permit the recording of SWS. Subjects were admitted to the study via emergency room admission and were given their first experimental dose of alcohol within 12 h of their last drink. They were thus studied after a prolonged period of intoxication. REM sleep was not completely suppressed by drinking in this context. REM sleep also did not rebound upon withdrawal. Instead, it presented gradual recovery that began at around 4 days of abstinence. Somewhat paradoxically, SOL was very fast on the first withdrawal night but then increased dramatically, only normalizing after 1 week of abstinence. WASO and N1 sleep did not appear to be affected much by drinking or withdrawal (Supplementary Table S6).

Gross et al. [55] studied four alcoholic men after 6 days of in-patient treated abstinence. The subjects were studied under two conditions in a counterbalanced design. They spent 15 days in a "wet" condition in which they had a baseline of 3 days with no alcohol, followed by 1 day of alcohol adaptation, 4 days of "alcoholization," 3 days of withdrawal, and 4 days of "recovery." The alcoholization days consisted of heavy drinking with an average consumption of 3.1 g/kg. The dry condition consisted of the number of nights but with no alcohol adaptation or heavy drinking. Data from the wet and dry conditions were then compared across the same nights in the sequence. SOL increased with alcohol and during initial withdrawal relative to baseline and recovery. SWS increased with alcohol but was lower than baseline during initial withdrawal and recovery. REM sleep was suppressed when drinking but did not show a rebound during withdrawal or recovery relative to baseline (Supplementary Fig. S1).

Lester et al. [56] studied 17 male alcoholics for two baseline nights after at least 3 weeks of sobriety and for two nights (alcohol) following days in which they drank from 1300 until 2100 hours with bedtime blood alcohol levels of 0.15 g% and then for two nights following withdrawal (recovery) and a subsequent night after a further week of abstinence. Data were reported separately for the first and second halves of the night. WASO and N1 decreased with alcohol and then returned to baseline. %REM in the first half of the night decreased from 18.6% at baseline to 12.1% while drinking and returned to 19.3% in withdrawal. In the second half of the night, it decreased from 33.9% at baseline to 12.1% while drinking and partially recovered to 19.3% during withdrawal. Slow-wave sleep showed a dramatic increase while drinking and recovery to slightly above baseline for the first half of the night and substantially above baseline for the second half of the night when measured during withdrawal (Supplementary Table S7).

Wagman and Allen [57] studied six male alcoholics who had been sober for at least 7 days. Data were collected at baseline and then during 5 days of receiving 18 ounces of 95% proof alcohol, followed by 5 days of 26 ounces and then at least 1 day of 32 ounces. Data were then collected after 1 week of abstinence. Only SWS data were reported. The baseline value of ~3% SWS increased to ~10% at 18 ounces and then to around 13% at 26 ounces and 16% at 32 ounces, dropping back to 5% after 1 week of no alcohol.

Gross and Hastey [58] studied 10 young male alcoholics for a baseline period of ~3.5 weeks postadmission. Following the baseline, they received alcohol (1.6 g/kg on day 1 and 3.2 g/kg on subsequent days) for either 5 or 7 days. They were then denied alcohol and studied for 7 days of withdrawal. They were somewhat arbitrarily divided into two groups based on the percentage of SWS on the baseline nights. The "low" group had SWS values between 14 and 29%, and the "high" group had SWS values between 32 and 44%. In both groups, %SWS was elevated while drinking relative to baseline and dropped to below baseline levels upon withdrawal from alcohol, with the appearance of a gradual recovery over days of abstinence (Supplementary Fig. S2).

Although the focus of the study was on SWS, the authors reported REM data during withdrawal relative to the values that were seen at baseline and the minimum value that was seen while drinking. REM sleep dropped to zero in both groups at some point over the drinking nights and recovered to baseline (or slightly less than baseline) on the first withdrawal night. For the low SWS group, REM sleep exceeded baseline on the second withdrawal night (Supplementary Fig. S3).

The general trends of drinking and withdrawal effects on sleep variables are summarized in Table 7. Although some variability is

Table 7. Summary of trends from studies in which alcohol was administered to AUD patients and then withdrawn

	SOL		WASO		N1		SWS		REM	
	Drinking	*Withdrawn*	*Drinking*	*Withdrawn*	*Drinking*	*Withdrawn*	*Drinking*	*Withdrawn*	*Drinking*	*Withdrawn*
Johnson et al. [53]		Δ		∇		∇		∇▲		Δ
Allen et al. [54]		▼Δ▼		∇		▼				∇▲
Gross et al. [55]		←→					▲	∇	▼	←→
Lester et al. [56]			▼	▲	▼	▲	▲	▼	▼	Δ
Wagman and Allen [57]							▲	▼		
Gross and Hastey [58]							▲	▼	▼	▲

Closed triangles indicate strong effects, and open triangles indicate weaker effects in the direction indicated. Drinking effects are indicated relative to baseline. Withdrawal effects are indicated relative to drinking. ←→, no effect observed. Multiple triangles reflect the magnitude and direction of effects that differed in different stages of withdrawal (e.g., ▼Δ▼ indicates a strong decrease followed by a weaker increase followed by a strong decrease)

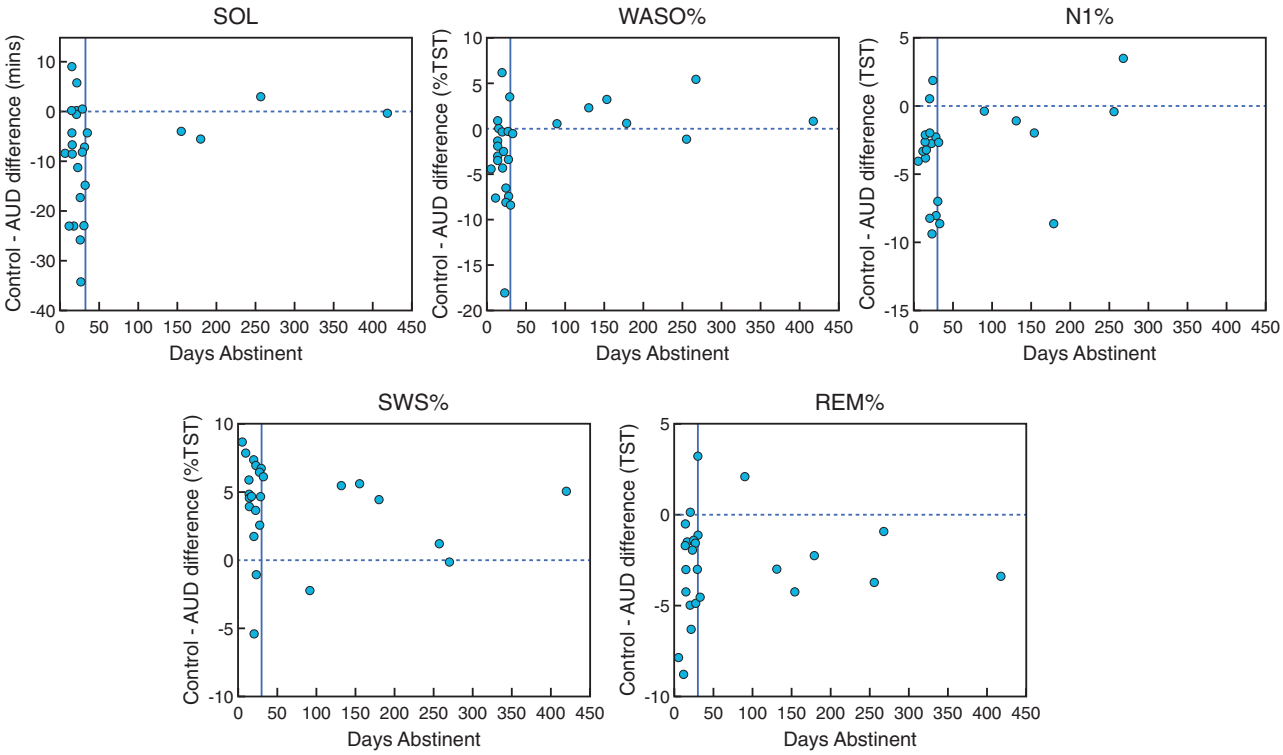

Fig. 3 Difference scores between control and AUD values for sleep onset latency (SOL) and the percentage of total sleep time (TST) spent awake (WASO%), N1 sleep (N1%), slow-wave sleep (SWS%), and REM sleep (REM%). The dashed horizontal line marks the point of no difference between controls and AUD. The solid vertical line marks the 30 boundary between short- and long-term abstinence. Data are presented as a function of the length of time abstinent

observed, as with the data above in normal controls, administering alcohol to AUD patients leads to an increase in SWS that then subsequently decreases upon withdrawal. Likewise, drinking decreases (but does not entirely suppress) REM sleep, with some variability in recovery upon withdrawal. The *binge/intoxication* effects on sleep are summarized in Fig. 1.

SLEEP IN RECENTLY SOBER AUD: *WITHDRAWAL/NEGATIVE AFFECT* DOMAIN

Withdrawal/negative affect: effects on sleep

In AUD patients, their ubiquitous, chronic, and long-lasting sleep issues are a cause of negative affect. Some of the reported high comorbidity of insomnia and alcoholism [59] may be attributable to poor sleep habits and irregular sleep-wake schedules that are an inevitable consequence of drinking. Changes in brain structure, function, and neurochemistry [5] may also play a role. Certainly, the incidence of insomnia in AUD has been reported to be as high as 91% [60].

For the purposes of this review, recent abstinence is somewhat arbitrarily considered to be within the first 30 days, the typical duration of short inpatient treatment programs. Several studies are available in which AUD patients at different stages of abstinence (7–30 days) are compared with control subjects (typically non-AUD social drinkers) [56, 61–72]. Data that are presented in this section thus reflect differences between AUD and control data relative to the time of abstinence in the AUD groups.

SOL for abstinent AUD in these studies ranged from 35.1 min longer to 8.3 min shorter than controls and was an average of 10.6 ± 12.2 min longer [56, 61–72]. WASO% for abstinent AUD ranged from 5.7% less to 18.6% more than in controls and was an average of 4.1% ± 5.1% more. N1% in abstinent AUD ranged from 1.6% less to 9.7% more than in controls and was an average of 3.7% ± 2.9% more. Short-term abstinent AUD individuals take longer to get to sleep and have more time awake or in N1 drowsiness (Fig. 3). In the same studies, SWS% in abstinent AUD ranged from 5.6% higher to 8.6% lower than in controls with a median of 4.5% lower (and 15 of the 17 datasets showed AUD lower than controls). Finally, REM sleep in abstinent AUD ranged from no difference to 9% more than in controls and with a median of 3.1% more. Short-term abstinent AUD subjects took longer to get to sleep and had more time awake or more time in N1 drowsiness. Figure 3 shows the values for each of these variables as a function of the average number of days abstinent in each of the studies from which they were drawn. What is apparent is that for all of these measures, data are highly variable, and there is no trend toward recovery within 30 days.

Withdrawal/negative affect: effects on EEG

The spectral analysis of sleep EEG data was conducted within 30 days of withdrawal in fewer studies. Consistent with reports of a reduction of SWS, Irwin et al. [66] reported significantly lower NREM delta power (0.75–4 Hz) across the entire night in alcoholics who were abstinent for ~30 days relative to controls, particularly in the first NREM period. Irwin et al. [67] studied the impact of sleep deprivation on SWS and delta EEG power in European American and African American subjects. Both AUD groups (abstinent before testing for on average of 23 days) showed a decrease in delta power relative to controls in the baseline condition, an effect that was more pronounced in the African American AUD group. Importantly, neither AUD group showed the typical increase in delta power during the recovery night following sleep deprivation (which was observed in their respective control subjects). They also saw a trend toward higher beta activity in alcoholics across the entire night at baseline that became a significant difference during a recovery night following a night of partial sleep deprivation.

Feige et al. [70] studied AUD subjects in the third week of an inpatient treatment program. Subjects with AUD were divided into two groups based on relapse status at 3 months posttreatment. The abstaining group had lower delta power compared with the relapsing group and controls in N2 sleep. They also reported higher beta activity during REM sleep in the relapsing group compared with the abstaining group and controls. Both effects, although significant, were small and inconsistent across two nights of measurement.

Singh et al. [72] studied AUD subjects after 2–3 weeks of treatment and a further week of washout from lorazepam. EEG analysis was conducted during early NREM sleep (N1+N2), SWS, and REM sleep at left and right frontal, temporal, parietal, and occipital sites. Delta power was lower in patients during N1+N2 and SWS at the left and right temporal sites and right parietal and occipital sites. Alpha power increased in patients during N1+N2 at the left occipital site, where 30–50 Hz activity was also elevated during SWS. REM sleep displayed higher beta activity in patients bilaterally at all sites and higher 30–50 Hz activity at right parietal and occipital sites.

Another approach to measuring the brain's ability to generate delta frequency responses is via auditory evoked responses. A proportion of stimuli will elicit a single delta waveform response, known as a K-complex [73]. K-complexes behave much like SWS and delta power, in which their amplitude decreases with aging [74], and differences between subjects are at least partially attributable to differences in cortical gray matter volume [75]. We recently conducted a study in which 16 AUD subjects were initially studied at an average of 17 days of abstinence and then 1 month and 3 months after the first assessment [76]. Control subjects were also studied at each time point. At the initial assessment, both the proportion of trials in which K-complexes were elicited (a measure of the facility of the brain to generate delta activity) and the amplitude of the averaged K-complex response significantly decreased in AUD. The *withdrawal/negative affect* effects on sleep are summarized in Fig. 1.

LONG-TERM SLEEP EFFECTS IN ABSTINENT AUD: *PREOCCUPATION/ANTICIPATION* DOMAIN

Preoccupation/anticipation: effects on sleep

A few studies investigated sleep in AUD subjects who were abstinent for >30 days [61, 65, 77–80]. These data are also shown in Fig. 3.

The ideal design for studying the effects of long-term abstinence includes longitudinal assessments that are conducted within the same subjects at increasing lengths of time sober. Rundell et al. [61] studied 20 AUD subjects near the beginning and again near the end of a 13-week treatment program and compared them to 20 age-matched controls. SOL, N1%, and REM sleep were elevated, and SWS decreased at both time points compared with controls. Some evidence of recovery in SWS and REM sleep was observed at the second time point. A subset of six subjects was studied 6 months after release from the hospital. For these subjects, SWS showed further recovery at 6 months but was still lower than control values. SOL and REM sleep exhibited no further recovery from 12 weeks to 6 months.

Williams and Rundell [77] studied 46 AUD subjects in two sessions: the first at 35 days sober and the second at 92 days sober. SOL was elevated relative to controls at 35 days, with some partial recovery at 92 days. N1% remained elevated at both time points. SWS% was lower and REM% was higher in AUD subjects than in controls at 35 days. Both variables showed only partial recovery to control values at 92 days. Twenty-four subjects returned for a third session 9 months after entering the program. Of these, 14 had resumed drinking, and 10 remained abstinent. These data are difficult to quantify because the earlier time points were not separated into these groups. At 9 months, however, the abstaining AUD subjects had reductions of % WASO and N1% and more SWS than those who were released. REM sleep in relapsed AUD subjects was lower than in control subjects.

Drummond et al. [65] studied 29 AUD subjects at 16 days sober and again at 19 weeks sober and a group of age-matched controls. SOL was higher in AUD subjects than in controls at both time points. WASO remained elevated at 16 days but decreased at 19 weeks. REM sleep remained elevated at both time points, and SWS was suppressed at both time points. Nine sober AUD subjects returned for further evaluation at 14 months. These subjects showed no further improvements in sleep values compared with subjects at 19 weeks.

When these data are combined with those of others with a single time point [78–80], the following patterns emerge. SOL for abstinent AUD in these studies ranged from 15.8 min longer to 2.4 min shorter than controls and was an average of 5.44 ± 5.72 min longer. WASO% for abstinent AUD subjects ranged from 5.1% less to 8.7% more in controls and was, on average, recovered to control values (0.27% ± 5.1% less). N1% in abstinent AUD subjects ranged from 3.3% less to 9.0% more than in controls and was an average of 3.0% ± 4.1% more. SWS% in abstinent AUD ranged from 2.4% higher to 6.5% lower than in controls and was an average of 3.7% ± 3.1% lower. Finally, REM sleep in abstinent AUD subjects ranged from 3.0% less to 4.7% more than in controls and was an average of 1.9% ± 2.7% more. Figure 3 shows the values for each of these variables as a function of the average number of days abstinent in each of the studies from which they were drawn.

Preoccupation/anticipation: effects on EEG

EEG spectral analysis was conducted in 14 AUD subjects and matched controls by Irwin et al. [79] at 31 ± 28 days sober for data that were collected in the first sleep cycle. During NREM and REM sleep, delta and theta activity was significantly less in AUD subjects. Beta activity was significantly less in NREM sleep, with a trend toward a decrease in REM sleep. Colrain et al. [80] reported spectral analysis data from multiple EEG sites in male AUD subjects who had been sober for an average of 156.6 ± 161.8 days and female AUD subjects who had been sober for an average of 258 ± 217.1 days. Relative to controls, alcoholics had significantly lower NREM sleep across the whole night and in the first NREM period in the slow (<1 Hz) band and in each of the 1 to <2, 2 to <3, and 3 to <4 Hz delta EEG bands. The slower end of theta activity (up to 6 Hz) displayed a similar pattern to delta frequencies. The effects were more prominent in frontal than posterior scalp derivations in alcoholic men and women. The delta effects were not seen in REM sleep. They did not report any differences in alpha or beta activity during sleep.

Two studies evaluated sleep evoked delta responses in AUD. Nicholas et al. [81] studied seven AUD subjects who had been abstinent for 70–726 days who met the DSM-IV criteria [82] for alcohol dependence and eight normal control men. Subjects with AUD were significantly less likely to generate a K-complex in response to a tone and had significantly smaller amplitude responses. In a larger study, Colrain et al. [83] studied 42 abstinent long-term alcoholics (27 men) and 42 controls (19 men). These subjects were the same as those reported in Colrain et al. [80] above. Subjects with AUD were significantly less likely to produce K-complexes than controls. Frontal (but not posterior) amplitude of the average response was significantly smaller in AUD subjects. A subset of 15 of the AUD subjects was followed for a further 12 months and had significantly higher amplitudes of the average K-complex response [84]. Finally, in the Willoughby et al. study [76] above, no further recovery was observed in either the proportion of trials in which K-complexes were elicited or the amplitude of the average K-complex response at 3 months sober over that seen at 1 month sober. The *preoccupation/anticipation* effects on sleep are summarized in Fig. 1.

SEX DIFFERENCES IN SLEEP INTERACTIONS WITH ALCOHOL AND AUD

Few studies have investigated the influence of sex differences on the ways in which drinking to intoxication, withdrawal, and protracted abstinence affect sleep. Sex differences have been reported in drinking patterns and pharmacokinetics of alcohol. Women tend to have less body water and more body fat than men and thus tend to have higher blood alcohol levels than men after consuming the same amount of alcohol because of alcohol's hydrophilic properties [85]. Historically, AUD has been around five-times more prevalent among men than among women, but the gender gap is decreasing with regard to both alcohol consumption and AUD, at least in the United States [86, 87], including binge drinking [88]. Women are more vulnerable to the development of alcohol-related diseases, such as liver cirrhosis [89], cardiomyopathy [90], and cancer [91]. Alcohol-dependent women have worse quality-of-life scores than alcohol-dependent men [92]. However, although the risk of developing insomnia is 1.41-times higher in women [93], no sex differences were found in the frequency of insomnia in men and women who underwent treatment for alcohol dependence [94].

As shown in Table 1–6, most studies of the effects of acute alcohol on sleep either did not investigate female subjects or had sample sizes that were too small to evaluate possible sex differences in the data. The two studies with sufficient numbers of men and women reported different results. Arnedt et al. [40] found that drinking to intoxication resulted in more sleep disturbances (i.e., decrease in sleep efficiency and increase in wakefulness) but a similar impact on sleep architecture (i.e., %SWS and %REM sleep) in healthy women compared with men. However, Chan et al. [42] found no sex differences in the effects of alcohol on sleep in older adolescents.

Most studies of early withdrawal and extended abstinence have also either used only male subjects or did not evaluate sex differences. Colrain et al. [80] reported that women had better sleep efficiency and more delta activity during NREM sleep than men, regardless of diagnosis, and that men with AUD appeared to present a more pronounced reduction of delta activity during NREM sleep than women with AUD. Furthermore, estimated lifetime alcohol consumption predicted the percentage of SWS in men with AUD but not in women with AUD. Estimated lifetime alcohol consumption was higher in alcoholic men than in alcoholic women, and the women had longer periods of sobriety prior to testing.

With the growing prevalence of AUD in women, studies need to include larger samples of men and women with AUD to further evaluate possible sex differences in the effects of drinking to intoxication, alcohol withdrawal, and protracted abstinence on sleep.

POSSIBLE NEUROCHEMICAL MECHANISMS OF THE EFFECTS OF ALCOHOL ON SLEEP, PARALLELED BY NEUROCHEMICAL CHANGES ACROSS THE ADDICTION CYCLE

Sleep is associated with a complex set of interactions between two major neurotransmitter systems: acetylcholine and norepinephrine (for review, see [95, 96]). For example, NREM sleep is a period during which cholinergic and noradrenergic brainstem arousal mechanisms are dramatically reduced. The transitions between NREM and REM sleep involve a complex interaction between REM-on and REM-off neuronal groups in the brainstem. REM-on groups largely consist of cholinergic cells in the lateral dorsal tegmentum (LDT) and pedunculopontine tegmental nucleus (PPT). REM-off cells involve serotonergic neurons in the dorsal raphe nucleus and noradrenergic locus coeruleus. A set of reciprocal interactions between the two groups of neurons, whereby REM-on neurons are influenced by a self-excitatory loop but also have an excitatory link to REM-off neurons, has long been hypothesized, a model that was originally developed by McCarley and Hobson [97]. REM-off cells dominate once a threshold of activation is reached, and they have an inhibitory action on REM-on cells but are also part of a self-inhibitory feedback loop that progressively decreases their activity. Eventually, REM-off cell activity drops below a threshold, and REM-on cells regain dominance.

Alcohol interacts with both cholinergic and noradrenergic brainstem systems but possibly via some of the same neurotransmitter circuitry that is involved in mediating the incentive salience/pathological habit, reward deficit/stress surfeit, and executive function domains that are described above. For the purposes of this review, we explore the effects of alcohol on the neurotransmitter systems that are considered key to the addiction cycle outlined above.

Neurochemistry of sleep relevant to the binge/intoxication stage

GABA. The acute effects of alcohol on decreasing sleep latency, increasing SWS, and increasing EEG delta power can possibly be explained by the GABA receptor agonist properties of alcohol. Alcohol exposure leads to the presynaptic release of GABA throughout the CNS. Within the thalamus, the hyperpolarizing effect of GABA causes the opening of low-threshold Ca^{2+} ion channels and a pattern of synchronized burst firing that manifests as sleep spindles on the sleep EEG. The further release of GABA causes greater levels of hyperpolarization and the production of

delta EEG waveforms [98]. The subsequent withdrawal of tonic input to the reticular nucleus allows the release of GABA and inhibition of thalamo-cortical circuits [99]. These effects, plus the alcohol-induced release of GABA in the brainstem [100], may also play a role in alcohol's suppression of REM sleep in the context of high doses of alcohol.

The increase in delta activity that is produced by acute alcohol early in the night is also consistent with alcohol's GABA receptor agonist properties. EEG delta activity is partially mediated by the GABA-induced hyperpolarization of cortical and thalamo-cortical neurons [99]. There is evidence that acute alcohol modulates metabotropic glutamate receptor (mGluR)-mediated slow currents [2] that are thought to underlie the slow oscillation of thalamo-cortical cell activity that underlies delta generation [101]. Further hyperpolarization can lead to the cessation of spindle activity and the development of delta activity [102]. Sleep spindles (associated with sigma frequency power) are produced when thalamo-cortical cells become hyperpolarized, resulting in low-threshold spikes and the generation of spindle frequency activity in thalamic reticular cells [102]. Alcohol consumption causes a decrease in sigma power [50], but benzodiazepines cause spindle and sigma facilitation [103]. These findings are consistent with older data that show inverse effects of benzodiazepines on sigma and delta activity [104]. Recent work identified an important role for GABAergic interneurons that act to facilitate the REM-off process [105]. Alcohol may influence this REM-off process through its effects on GABA, leading to the suppression of REM sleep in the short-term.

Dopamine. Historically multiple neurotransmitter systems—norepinephrine, serotonin, acetylcholine, histamine, adenosine, hypocretin/orexin, and dopamine—have been studied in the context of behavioral arousal. Neurons in the locus coeruleus, dorsal raphe nucleus, and tuberomammillary nucleus fire fastest during wakefulness, slow during non-REM sleep, and nearly stop firing completely during REM sleep. Cholinergic neuron firing contributes to arousal and REM sleep. However, these neurotransmitter systems are only indirectly related to the acute reinforcing effects of alcohol. In contrast, the mesocorticolimbic dopamine system plays a key role in incentive salience and begins the process of pathological habits [106]. However, its role in sleep-wake regulation has been scarcely studied. The dopamine neuron firing rate varies little between sleep and wake states [107, 108], although lesions of dopamine cell groups in the ventral tegmentum that project to the forebrain significantly reduced behavioral arousal in rats [109]. Parkinson's disease patients, who exhibit pronounced dopamine lesions, experience severe sleep disorders [110, 111]. Dopamine D_1 and D_2 receptors have been clearly implicated in the induction of hyperarousal [112]. The existence of sleep state-dependent dopaminergic neurons has been reported in the ventral periaqueductal gray [113]. The presynaptic activation of dopamine transmission is a key pharmacological property that mediates the wake-promoting effects of stimulants [114, 115]. Thus, dopamine may play a role in sleep regulation at least indirectly through arousal mechanisms via the mesocorticolimbic dopamine system and possibly more directly via dopamine networks that are outside of the classic mesocorticolimbic dopamine system.

Opioid peptides. Alcohol at intoxicating doses releases opioid peptides that interact with the same receptors as opioid drugs [116]. Opioids increase wakefulness and decrease REM sleep [3, 117]. In rats, low doses of morphine decrease sleep behavior, measured by EEGs of NREM sleep, REM sleep, and sleep efficiency [118]. The morphine-induced inhibition of REM sleep was localized to the medial pontine reticular formation in cats [119]. This observation was replicated in cats for selective μ but not δ or κ opioid receptor agonists [120]. In rats, a μ opioid receptor agonist increased wakefulness when injected in the ventrolateral preoptic nucleus, and infusion of the selective μ opioid receptor antagonist CTAP in the ventrolateral preoptic nucleus promoted sleep, suggesting that endogenous μ opioid receptor agonists may participate in maintaining arousal via the ventrolateral preoptic nucleus [121]. However, the microinjection of μ opioid receptor agonists in the nucleus of the solitary tract produced SWS [122], suggesting a μ opioid receptor interaction with other sleep-regulatory systems.

In terms of how endogenous opioids interact with sleep disturbances that are produced by AUD, chronic opioid use has been hypothesized to cause sleep disturbances and excessive daytime sleepiness and fatigue [123]. Sleep architecture studies have revealed different effects of morphine-like opioids that depend on the phase of opioid use [3]. During the induction phase, the use of morphine-like opioids significantly disrupts sleep, reduces REM sleep and SWS, and increases wakefulness and arousals from sleep. During the maintenance phase of opioid use, decreases in SWS and REM sleep and increases in wakefulness tend to normalize. During the withdrawal stage, significant insomnia is a major complaint during chronic opioid withdrawal, accompanied by frequent arousals and decreases in REM sleep [3]. During the protracted abstinence phase after chronic methadone use, TST significantly increased with rebound SWS and REM sleep that lasted for months following withdrawal with chronic methadone use [124].

Neurochemistry of sleep relevant to the withdrawal/negative affect stage

GABA within-system neuroadaptations. Sleep EEG effects in individuals with long-term alcohol dependence are opposite to those after acute alcohol administration. One possible mechanism involves within-system neuroadaptations even during the course of a bout of intoxication as discussed above. Chronic alcohol-induced alterations of the responsiveness of GABA mechanisms include the allosteric modification of GABA receptors [7, 8] and a reduction of $GABA_A$ receptor function [7, 125] in rodent models of alcohol dependence. Thus, the downregulation of brainstem GABAergic systems following the development of alcohol dependence leads to the diminished activity of REM-off systems and subsequently a greater propensity for REM sleep. The downregulation of GABA systems could also partially explain the decrease in both delta power and the amplitude of evoked delta responses in abstinent alcoholics. However, there are other possible within-system mechanisms that may contribute to the disruption of sleep architecture during acute withdrawal and protracted abstinence. For example, the loss of dopamine function during acute withdrawal may contribute to malaise and hypoarousal that also could result in rebound sleepiness in late withdrawal.

Hypocretin between-system neuroadaptations. With regard to between-system neuroadaptations, all of the neurotransmitter systems that are hypothesized to act in the extended amygdala to promote negative emotional states are potential targets for between-system opponent processes that could contribute to sleep disturbances in the *withdrawal/negative affect* stage. These include (in order of sleep-related prominence) hypocretin, norepinephrine, glucocorticoids, and neuroimmune factors.

Hypocretin/orexin peptides have been implicated in sleep-wake regulation since their initial discovery [126]. They have wide projections in the brain [127], interacting with autonomic, neuroendocrine, and neuroregulatory systems [128–135]. Perhaps most well known is that the hypocretin system makes a key contribution to the etiology of narcolepsy. In two different animal models with impairments in the hypocretin/orexin system (i.e., genetic narcoleptic dogs with a mutation of the hypocretin receptor 2 [Hcrt-2] gene [136] and mice with a null mutation of the preprohypocretin gene that produces hypocretin-1 and hypocretin-2 peptides [137]), symptoms of narcolepsy were observed,

suggesting that impairment of the hypocretin/orexin system may underlie the syndrome of human narcolepsy. Human narcoleptic patients presented dramatic reductions (85–95%) of cerebrospinal fluid hypocretin-1 [138] and the number of hypocretin neurons [139, 140], leading to the hypothesis that narcolepsy could be related to the ongoing loss of hypocretin neurons [141].

Hypocretins modulate key sleep systems, including norepinephrine [130, 142–144] and acetylcholine [145]. Hypocretins also modulate serotonergic [146, 147], histaminergic [148], and dopaminergic systems [149, 150] and the hypothalamic-pituitary-adrenal (HPA) axis [151–153]. The hypocretin/orexin system stabilizes the firing of brainstem neurons that control wakefulness and REM sleep (cholinergic in the LDT/PPT, noradrenergic in the locus coeruleus). Notably, hypocretin neurons discharge during waking, especially with movement [154, 155]. Thus, unsurprising is that when these neurons are lost, such as in narcolepsy, patients present excessive daytime sleepiness and frequent sleep attacks.

The hypocretin/orexin system is thought to be a key regulator that stabilizes the firing of brainstem neurons that control wakefulness [156]. The silencing of hypocretin neurons using optogenetics or DREADDs that allow the modulation of neural activity with the temporal resolution of several hours, induces sleep during the light phase but not during the dark phase [157, 158] (although this approach may also affect other neurotransmitter systems). This supports the hypothesis that the hypocretin system acts as a regulator of behavioral states by modulating the arousal threshold [126] so that the organism can maintain appropriate and adequate wakefulness to cope with fluctuations of external and internal environments [156]. The overactivation of hypocretin/orexin peptides during drug withdrawal may cause destabilization of the boundaries between arousal sleep states that are found in acute and protracted abstinence. Numerous rodent studies have shown that hypocretin-1 receptor antagonists decrease high levels of alcohol self-administration in alcohol-preferring rats, the motivation to seek alcohol, alcohol drinking in dependence, and the cue-induced reinstatement of alcohol seeking [4, 159, 160].

Norepinephrine between-system neuroadaptations. Norepinephrine has long been associated with promoting wakefulness. This action of norepinephrine in vivo likely involves the activation of α_1 adrenergic receptors, in which drugs that antagonize α_1 adrenergic receptors facilitate sleep onset [161]. This is likely a postsynaptic action of norepinephrine, whereas α_2 adrenergic receptor antagonists, which presynaptically increase norepinephrine release, delay sleep. In contrast, α_2 adrenergic receptor agonists inhibit norepinephrine release and decrease wakefulness [161, 162]. Drugs that block the uptake of norepinephrine increase or prolong wakefulness [163]. Neurochemical microdialysis studies have shown that extracellular levels of norepinephrine decrease in the transition from wakefulness to sleep [164, 165], and lesions of neurons in the locus coeruleus decrease waking [166].

Noradrenergic systems have also long been associated with alcohol dependence. Adrenergic receptor antagonists decreased dependence-induced drinking in rats. Although the locus coeruleus may not be directly implicated in the negative emotional states that are associated with alcohol withdrawal and protracted abstinence, sub-coeruleus noradrenergic projections to the bed nucleus of the stria terminalis modulate negative emotional states that are associated with opioid withdrawal and protracted abstinence [167].

Glucocorticoids, CRF, and vasopressin between-system neuroadaptations. One of the major bodily responses to acute stress that is associated with alcohol withdrawal is an elevation of glucocorticoids and the concomitant activation of extrahypothalamic stress systems [10]. The chronic ingestion of alcohol leads to a blunted HPA response that reflects negative feedback on the hypothalamic control of the HPA axis by CRF. However, at the same time, glucocorticoids sensitize the extrahypothalamic CRF system in the extended amygdala [168]. Both of these responses can contribute to the effects of alcohol in the *withdrawal/negative affect* stage of the addiction cycle.

Excessive activation of the HPA axis induces sleep debt [169], and sleep debt increases cortisol levels [170]. Patients with insomnia without depression presented high levels of cortisol, mainly in the evening and at sleep onset [171]. In clinical practice, the use of pharmacological doses of glucocorticoids is associated with sleep disturbances [172]. When steroids were administered as a short-term treatment in a multicenter, placebo-controlled study for optic neuritis, insomnia was one of the most commonly reported side effects [173]. Others have seen in humans a marked drop of cortisol levels during napping, followed by a transient increase during the postnap period [174]. The administration of glucocorticoids in humans can significantly suppress REM sleep [175] and cause a modest increase in SWS [176]. Altogether, human studies suggest that the HPA axis may contribute to the initiation and perpetuation of chronic insomnia [170].

An increase in cortisol may also be a marker of CRF and norepinephrine activity during the night, particularly because glucocorticoids can drive extrahypothalamic CRF activation. The intracerebroventricular administration of CRF increases EEG frequency and wakefulness and decreases SWS [177]. Other studies that reported decreases in SWS with elevated cortisol levels may indicate excessive glucocorticoid receptor activation in the amygdala, presumably via CRF. These positive feedback effects are opposite to the known inhibitory actions on CRF that are found in the paraventricular nucleus of the hypothalamus and anterior pituitary [176].

Chronic exposure to excess glucocorticoids is a key part of Cushing's syndrome. Consistent alterations of sleep (e.g., decrease in SWS, increase in sleep latency, increase in wake time, decrease in REM latency, and increase in REM density) have been reported In Cushing's syndrome with PSG recordings [178]. Given the hormonal and affective profiles that are common in Cushing's syndrome and severe AUD, one could argue that the CRF-HPA axis may contribute to sleep disturbances that are associated with AUD, and sleep disturbances may contribute to dysregulation of the CRF-HPA axis in a feed-forward allostatic framework.

Arginine vasopressin (AVP) is also involved in the regulation of adrenocorticotropic hormone (ACTH) secretion and consequent glucocorticoid release [179]. Similar to CRF, AVP serves extrahypothalamically as a neurotransmitter [180]. A human study reported the sleep-associated inhibition of stimulated ACTH and cortisol release, suggesting a period of lower responsiveness of the pituitary-adrenocortical axis to AVP during early sleep [181]. Given the parallels between CRF and AVP in controlling the HPA axis and sleep regulation and given the role of CRF, glucocorticoids, and vasopressin in excessive drinking that is associated with alcohol dependence [168, 182], one could speculate on similar parallels in extrahypothalamic control over sleep and possible alcohol interactions.

Neuroimmune between-system neuroadaptations. Cytokines are intercellular signaling peptides that are released by immune cells, neurons, and astrocytes and have been hypothesized to be activated during alcohol withdrawal [95, 183] and also influence sleep [161, 184], albeit via actions on possibly different circuits. During infections, bacterial cell wall products, such as lipopolysaccharide, may trigger the production of cytokines that then increase NREM sleep and reduce REM sleep [185]. Several cytokines, including interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α), promote sleep [184, 186]. The administration of IL-1β and TNF-α in the preoptic area in rats reduced firing rates of wake-active neurons and promoted NREM sleep. IL-1β injections in the locus coeruleus [187] and dorsal raphe nuclei [188] promoted NREM sleep [184, 189, 190]. A physiological role for IL-1β and TNF-α

signaling in sleep can be argued based on observations in which the blockade of IL-1β and TNF-α signaling via the deletion of their receptors reduced spontaneous NREM sleep [191, 192]. Consistent with this hypothesis, cytokine levels in young, healthy individuals peaked during sleep [193], and a temporal relationship was found between sleep and IL-1β activity [194]. In a study of circadian patterns in humans, IL-6 was secreted at baseline in a biphasic circadian pattern, with a late-night peak [195].

A direct interaction between cytokines, sleep, and AUD was demonstrated by the observation that administration of the TNF-α antagonist etanercept led to the normalization of REM sleep in 18 abstinent alcoholics [196]. Cytokines have been implicated in negative emotional states that drive negative reinforcement in animal models of alcohol dependence [197] and may contribute to the activation of CRF systems in the extended amygdala during alcohol dependence [198].

Neuropeptide Y and endocannabinoid between-system neuroadaptations. Both NPY and endocannabinoids have been implicated in neuroadaptations that are associated with the development and persistence of alcohol dependence. Both neurochemical systems have been hypothesized to serve as a buffer to the activation of the brain stress systems during acute and protracted abstinence in alcohol dependence [24, 199]. Animal and human studies have reported sleep-promoting effects of NPY [200]. In animal studies, NPY increased EEG synchronization and increased sleep continuity [201, 202]. One mechanism that was hypothesized for NPY's sleep-promoting effects was a decrease in norepinephrine in the locus coeruleus [201]. Others have reported increases in wakefulness, activity, and eating with intracerebroventricular and intra-lateral hypothalamic administration of NPY in rats but an effect that was limited to this behaviorally active state [203, 204]. In humans, repeated intravenous NPY administration in young healthy subjects decreased sleep latency, decreased the first REM sleep period, and increased Stage 2 sleep time [205]. The secretion of cortisol and ACTH was blunted after NPY administration [205]. The sedative and anxiolytic-like effects of centrally administered NPY are consistent with its hypothesized anti-stress buffering role under environmental challenge and its hypothesized hypoactivity during alcohol withdrawal [206].

Marijuana and Δ^9-tetrahydrocannabinol are well documented to increase sleep in humans [207]. Endocannabinoids also increase sleep. More specifically, exogenously administered CB_1 receptor agonists enhance NREM sleep in rats and humans [208, 209]. The administration of CB_1 receptor antagonists increased wake time and reduced NREM sleep time in rats [210, 211]. Anandamide administration in the PPT decreased wakefulness and increased SWS, and these effects were reversed by a CB_1 receptor antagonist [212]. One hypothesis is that endocannabinoids act in the pons and medulla to enhance the release of acetylcholine [207].

In a study that employed a microanalysis approach to investigate the role of endocannabinoids in up-state/down-state transitions in sleep that were recorded from pyramidal neurons in the prefrontal cortex, the endocannabinoid system was shown to regulate up-states and sleep, serving as a neuromodulatory system that is intrinsic to cortical microcircuitry [213]. In this study, CB_1 receptor knockout mice exhibited an increase in wakefulness as a result of reductions of NREM sleep and NREM bout duration. During recovery from forced sleep deprivation, the knockout mice exhibited a reduction of NREM delta power and an increase in sleep fragmentation, consistent with increases in cortical excitability. The authors hypothesized that local neuromodulatory systems may tune network activity by regulating both excitatory and inhibitory neurotransmission within local cortical circuits, in which the activation of CB_1 receptor endocannabinoid signaling in layer 5 pyramidal neurons may serve to selectively decrease the efficacy of a subset of excitatory inputs [214]. Neuropeptide Y and endocannabinoids have been hypothesized to buffer increases in stress-like responses and increases in drinking during alcohol withdrawal in animal models of alcohol dependence [206, 215, 216], suggesting a common parallel neurochemical substrate for alcohol withdrawal-induced changes in sleep and alcohol seeking, albeit through different neurocircuits. Thus, the same opponent-process neurochemical actions that are produced during between-system neuroadaptations in the withdrawal/negative affect stage may be paralleled by actions on sleep systems that contribute to sleep disturbances in the withdrawal/negative affect stage.

Neurochemistry of sleep relevant to the preoccupation/anticipation stage

Glutamate. Glutamate neurons are ubiquitous in the brain and distributed throughout the forebrain and brainstem. They are hypothesized, together with GABA neurons, to comprise effector neurons that are associated with EEG changes that underlie sleep-wake states. Glutamate has been proposed to be the main regulator of arousal [1]. For example, the glutamatergic medial parabrachial nucleus in the dorsal pontine tegmentum that projects via the basal forebrain to the cerebral cortex regulates arousal [217]. In REM sleep, REM-on brainstem nuclei that contain acetylcholine, glutamate, and GABA promote activity in the basal forebrain and cortex and induce muscle atonia and rapid eye movements [218]. Fos-labeled neurons in the sublaterodorsal tegmental nucleus that trigger REM sleep were shown to be glutamatergic, measured by vGlut2 expression [219]. Finally, based on the anatomical and biochemical properties of astrocytes, others have proposed a mechanism by which astrocytes play a role as an energy provider through the release of lactate that is used as an energy substrate by glutamatergic neurons [220]. These results indicate that glutamate is a key player that drives the wake portion of the sleep-wake state.

However, the role of glutamate as a presumed sleep-wake effector neuron is more complicated, given the functional heterogeneity and intermingling of glutamate cell types in multiple regions, such that the stimulation of all glutamate neurons in any region may have opposing effects [221]. Nevertheless, a microanalysis of different effector neurons of sleep-wake states showed that 20% of Wake-max active (discharge maximally) cells were entirely glutamate-containing and also assumed to give rise to projections into the brainstem reticular formation and possibly spinal cord to influence behavior and EMG activity indirectly [221]. Indeed, the photo- or chemostimulation of genetically tagged glutamate neurons commonly evokes cortical activation [222, 223], likely reflecting the fact that glutamate is a prominent neurotransmitter by Wake/Paradoxical Sleep-max active neurons [221].

Chronic alcohol has long been associated with the dysregulation of glutamate activity, in which increases in glutamate function are associated with prolonged abstinence [224, 225]. Given the key role of glutamate in the neurocircuitry of relapse [226], cellular effects of alcohol on glutamate systems during protracted abstinence may generalize to the neurocircuits that drive sleep-wake transitions.

RELATIONSHIP BETWEEN TREATING INSOMNIA IN AUD AND ABSTINENCE

Insomnia and AUD

The previous section of this review focused on laboratory measures of sleep and showed that some PSG characteristics of sleep in AUD can persist for months or even years. However, insomnia is a subjective complaint, and its diagnosis does not require PSG to be conducted. Indeed, individuals with insomnia can sometimes have their symptoms masked by sleeping in an unfamiliar environment, such as a laboratory [227, 228].

The current definition of "insomnia disorder" is dissatisfaction with sleep despite having adequate opportunity for sleep that lasts

for 3 months and occurs three or more times per week. Insomnia is defined by difficulties in initiating sleep and/or maintaining sleep and/or early-morning awakening with an inability to return to sleep, and these sleep disturbances must cause clinically significant distress or impairments in daytime functioning. Importantly in the context of insomnia in AUD patients, the DSM-5 removed the distinction that was made in previous versions of the DSM between primary insomnia and comorbid insomnia. Similarly, the recent *International Classification of Sleep Disorders*, 3rd edition [229], grouped the secondary categories of insomnia and several subtypes ("psychophysiological insomnia," "idiopathic insomnia," "inadequate sleep hygiene," and "paradoxical insomnia") into a single category of "chronic insomnia disorder." For both groups, the diagnosis is made independent of PSG and based entirely on subjective reports by the patient. Severity can be measured by such instruments as the Insomnia Severity Index [230], in which subjects rate the perceived severity of their problems, indicate how much they interfere with daytime function, indicate how noticeable the sleep issues are to others, and indicate the extent to which they are worried by the condition.

There is a higher prevalence of AUD in insomnia patients than in good sleepers. For example, Ford and Kamerow [231] reported nearly double the prevalence of AUD in insomnia (7.0%) relative to those with no sleep complaints (3.8%). Weissman et al. [232] reported similar differences, with 3.3% of insomnia patients having AUD *vs*. 1.8% of normal sleepers. Notably, in a cross-sectional study of 1200 health maintenance organization members in Michigan, the prevalence of alcohol abuse or dependence was found to be 30% in those with insomnia. However, consistent with Ford and Kerow [231] and Weissman et al. [232], the gender-adjusted odds ratio for AUD was 2.0 (1.3–3.0) relative to those with no sleep disturbances [233].

Insomnia has a high prevalence in AUD [30]. Brower [234] compiled data from 13 studies across 3173 patients to yield a prevalence of 58.4%, although there was a large amount of variance in the data that the authors ascribed to such factors as differences in sample characteristics and the definitions that were used for both alcohol problems and insomnia.

Insomnia can precede AUD [233] and is also a symptom of alcohol withdrawal in both acute and protracted abstinence. Brooks et al. [235] studied 33 AUD patients on admission, during and 1 week prior to discharge from a National Institutes of Health clinical research inpatient treatment program. Twenty-eight patients also participated in a postdischarge study visit 4–6 weeks after discharge. Although the proportion of patients with a Pittsburgh Sleep Quality Index score >5 decreased from predischarge (69.7%) to post-discharge, both numbers were very high relative to the general population.

Persistent insomnia over months of abstinence has been observed in numerous studies [234]. In a study of 267 alcohol-dependent patients who entered inpatient and outpatient programs, 103 (47%) had baseline insomnia based on a questionnaire [236]. Even at the 6-month follow-up, 25% (26 of 103) showed persistent insomnia despite abstinence for the previous 3 months [236]. Such persistent sleep abnormalities in AUD have been validated by PSG measures [94]. Sleep architecture, such as an increase in the percentage of Stage 1 sleep (N1 or light sleep), a decrease in the percentage of N3 or SWS (deep sleep), and an increase in REM%, was observed up to 27 months [80, 94, 234]. These alterations of REM sleep, including an increase in REM% and a decrease in REM latency (minutes from sleep onset to the first REM period), were characterized as an increase in REM sleep pressure [237]. Under these conditions, patients may experience an increase in dreaming and/or an increase in vivid dreaming [234]. Polysomnographic measures and subjective reports also predicted relapse (for review, see [234]), as did the use of alcohol or hypnotics to help sleep upon admission to treatment [238].

Sleep interactions may not be restricted to AUD; they may also extend to risky drinking. Insomnia can precede and predict alcohol use in adolescents [239]. Poor sleep quality and insufficient TST have been shown to exacerbate associations between college drinking and negative drinking consequences of risky drinking [240–242]. In a 2-month prospective study of 157 college drinkers, students who reported higher sleep-related functional impairment experienced consistently high levels of negative drinking consequences, regardless of their risky drinking levels [242]. For a review of the relationship between sleep problems and adolescent AUD, see Hasler et al. [243]. Alcohol problem severity may also predict sleep disturbances. For problem drinkers, alcohol problem severity was predictive of the Pittsburgh Sleep Quality Index global score for sleep disturbance [244]. Intervention research suggests that targeting sleep problems among college drinkers may result in a decrease in alcohol use and related consequences [245, 246].

Treatment of insomnia and AUD

Sleep measures have also been included in numerous treatment studies and can provide some insights into whether treating insomnia in AUD contributes to abstinence or whether treating alcohol addiction improves sleep. One can divide such studies into two categories: those in which a sleep medication is applied to subjects with AUD and those in which an AUD medication is applied to treat AUD. The former category answers the question about whether treating insomnia contributes to abstinence.

As reviewed by Brower [234] and Chakravorty et al. [31], a number of randomized controlled trials have demonstrated that the treatment of insomnia and the treatment of AUD can be dissociated (Table 8). Some treatments that improve sleep in alcohol-dependent patients have no effect on drinking [247–249] or even worsen drinking [250]. Cognitive behavior therapy was shown to improve sleep but not drinking in two studies [247, 248]. Two drugs that improved sleep but not alcohol drinking include quetiapine [249] and trazadone [250].

Another rationale for the treatment of sleep disorders in AUD is that, retrospectively, subjects with AUD reported the presence of insomnia prior to the onset of AUD [251]. Many sleep studies have also revealed that sleep disturbances predict subsequent alcohol consumption in adolescents and adults [233, 252, 253]. One hypothesis for this association is that subjects may self-medicate their insomnia with alcohol [254, 255]. Finally, another benefit of treating insomnia is that it may provide symptom relief, improve quality of life, and improve functioning [234, 256].

Some investigators have argued that brief behavioral therapies are the treatment of choice for continued sleep disturbances during protracted abstinence because they have long-lasting benefits without causing negative effects on drinking outcomes [234]. One could argue that medications may work more quickly but inevitably alter sleep architecture themselves and have side effects, all of which may worsen drinking outcomes. One approach would be to use Food and Drug Administration (FDA)-approved medications with the least risk of side effects, including abuse potential, such as ramelteon and low-dose doxepin [234]. Non-prescription antihistamines may also work for some patients as alternatives to doxepin, which is also thought to work through the histaminergic system.

Treatment of AUD and insomnia

One reasonable conclusion is that if risky drinking and AUD cause insomnia and disturbances in sleep architecture, then successfully treating AUD would also treat sleep disturbances. However, such data are limited, largely because of the lack of studies and paucity of effective treatments for AUD. Acamprosate was approved by the FDA in 2004 as a medication for the treatment of AUD [257]. European trials of acamprosate for the treatment of AUD found a significant benefit for the maintenance of abstinence following

Table 8. Pharmacological and behavioral treatments for insomnia in alcohol dependence

Reference	Selected for insomnia	*n*	RCT	Daily dose, treatment duration	Primary outcome measure	Time since last drink	Effect on insomnia	Effect on drinking
Pharmacological								
Acamprosate								
Staner et al. [260]	No	24	Yes	1998 mg/day, 23 days	PSG	0	↓	∅
Perney et al. [261]	Yes[a]	239	Yes	2–3 g/day, 6 months	Short Sleep Index	≤10 days	↓	? ↓
Agomelatine								
Grosshans et al. [278]	Yes	9	No	25–50 mg/day, 6 weeks	Sleep Quality	NA	↓	NA
Chlormethiazole								
Gann et al. [279]	No	20	Yes	Taper protocol, 5 days	PSG	0	↑	NA
Gabapentin								
Karam-Hage and Brower [267]	Yes	15	No	Gabapentin 200–1500 mg, 4-6 weeks	SPQ	4 weeks	↓	↓
Karam-Hage and Brower [280]	Yes	50	No	Gabapentin (888 ± 418 mg) or trazodone (105 ± 57 mg), 4-6 weeks	SPQ	≥4 weeks	↓ G > T	↓ (2 subjects/ group)
Malcolm et al. [281]	No	68	Yes	Gabapentin/ lorazepam taper	Insomnia questions[b]	0	↓ G > L	∅
Brower et al. [268]	Yes	21	Yes	1500 mg, 6 weeks	PSG	≥1 week	∅	↓
Quetiapine XR								
Chakravorty et al. [282]	Yes	20	Yes	400 mg, 8 weeks	PSG	≥1 month	↓	NA
Ramelteon								
Brower et al. [283]	Yes	5	No	8 mg, 4 weeks	ISI	2–13 weeks	↓	Lapse to HD ($n = 1$)
Trazodone								
Le Bon et al. [284]	Yes	18	Yes	150–200 mg, 4 weeks	PSG	≥2 weeks	↓	NA
Friedmann et al. [250]	Yes	173	Yes	50–150 mg, 12 weeks	Sleep Quality	Immediate post-detoxification phase	↓	↑
Triazolam								
Fabre et al. [285]	Yes	12	No	0.5–1.0 mg, 28 days	Sleep diary and questionnaire	5-15 days	↓	? ↓
Behavioral								
Progressive relaxation (including muscle relaxation)								
Greeff and Conradie [286]	Yes	22	Yes	2 weeks	Quality of Sleep	≥1 month in RTP	↓	NA
Cognitive behavioral therapy for insomnia								
Currie et al. [248]	Yes	60	Yes	7 weeks	Sleep diary	≥1 month	↓	∅
Arnedt et al. [287]	Yes	7	No	8 weeks	Sleep diary	27-433 days	↓	↓
Arnedt et al. [247]	Yes	17	Yes	8 weeks	Sleep diary	8-433 days	↓	∅

The selection criteria were studies with sleep as the primary outcome
n number of subjects in the study, *RCT* randomized controlled trial, *SPQ* Sleep Problems Questionnaire, *PSG* polysomnography, *G* gabapentin, *T* trazodone, *L* lorazepam, *ISI* Insomnia Severity Index, *RTP* residential treatment program, *HD* heavy drinking, ↑ increased, ↓ decreased, ? unknown effect, *NA* not applicable, ∅ no difference, immediate post-detoxification phase, evaluated after 3–5 day detoxification protocol
[a]This was the secondary aim of this review, which is in itself a secondary analysis of data from a clinical trial
[b]Insomnia questions from the Clinical Institute Withdrawal Assessment Scale for Alcohol—Revised and Beck Depression Inventory. Table reproduced with permission from [31].

alcohol withdrawal in 15 of 18 randomized, double-blind, placebo-controlled trials [257]. In a large U.S. study, in which variables that were identified as important for treatment efficacy were applied as covariates and a subpopulation of individuals who were motivated to have a treatment goal of total abstinence at baseline were studied in a *post hoc* analyses, a significant linear treatment effect on the percentage of abstinent days was found that was consistent with prior positive studies [258]. Several studies, including a secondary analysis of the U.S. acamprosate study [258], showed that acamprosate may help normalize AUD-related sleep disturbances [259–261]. From a sleep architecture perspective, two of these studies showed that acamprosate improved sleep continuity, restored Stage 3 sleep, and increased REM sleep latency, all of which are related to relapse to AUD. There are no published studies of sleep measures with naltrexone and AUD [259, 260]. Sleep has not been studied in clinical trials of naltrexone, with the exception of one trial in which naltrexone was combined with gabapentin, thus confounding any

conclusions about the effects of naltrexone on sleep parameters [262]. One study reported positive effects of topiramate on both sleep and drinking [263, 264].

Another drug that has been shown to improve sleep and decrease alcohol drinking is gabapentin [265]. Gabapentin is an anticonvulsant that is approved by the FDA for neurogenic pain and restless leg syndrome. It is also on the Veterans Administration formulary for use as a secondary treatment for AUD (https://www.data.va.gov/dataset/va-national-formulary; accessed July 1, 2019). Gabapentin has been studied as a medication for the treatment of AUD, with positive results in double-blind, placebo-controlled human laboratory and clinical studies [258, 262, 265, 266]. In a landmark study, Mason et al. [265] showed that subjects who received gabapentin, particularly the 1800 mg daily dose, had better drinking and sleep outcomes. Gabapentin had a significant linear dose effect on increasing the rates of complete abstinence and no heavy drinking and sleep as measured by the Pittsburgh Sleep Quality Index total score over the 12-week course of treatment relative to placebo [265]. Gabapentin is also effective specifically for insomnia that is associated with alcohol dependence [267, 268]. One hypothesis is that gabapentin may be particularly helpful for substance use disorder patients who have an arousal, anxiety, and sleep disturbance component because it is used to treat restless leg syndrome and can improve drinking outcomes [234, 265]. Interestingly, the studies above that showed beneficial effects of gabapentin on AUD outcomes and sleep used immediate-release formulations, but a recent study that used an extended-release formulation did not show benefits for either AUD or sleep outcomes [269].

Nevertheless, given the paucity of data, it is difficult to dissociate the argument that treating sleep helps to treat alcohol addiction or that treating alcohol addiction helps to treat sleep disturbances. Obviously, the latter is a logical extension of considering sleep disturbances as a key symptom of protracted abstinence and a trigger for relapse. However, resolving these issues will require larger trials, more fine-grained analyses of sleep outcomes over time in clinical studies, the use of sleep-specific mediations (e.g., hypocretin receptor antagonists), and the advent of more medications that are effective in treating AUD. In this context, a clinical trial is about to begin in Australia, in which suvorexant, a hypocretin receptor antagonist, will be evaluated in terms of its ability to positively impact comorbid sleep disorder and AUD [270].

SUMMARY, CONCLUSIONS, AND OPEN RESEARCH QUESTIONS

Alcohol use disorder is a devastating chronic disease that has major negative impacts on the lives of patients and their families. The pathway to the development of AUD often involves binge drinking to high levels of intoxication that leads to a compulsion to consume it, the loss of control in limiting consumption, and a transition to the "negative reinforcement side" when consumption occurs to stave off the negative consequences of withdrawal. This cascade of events that occurs over an extended period of time has thus been framed as a three-stage cycle: *binge/intoxication*, *withdrawal/negative affect*, and *preoccupation/anticipation* ("craving"). These stages map onto the dysregulation of functional domains of incentive salience/habits, negative emotional states, and executive function.

There is a substantial body of scientific work that supports the hypothesis that AUD is a brain neurocircuitry disorder and that neuroadaptations within specific motivational circuits play an important role in defining and perpetuating the disorder. During the *binge/intoxication* stage, pathological habits are at least partially attributable to the excessive engagement of reward circuitry, leading to high incentive salience for such factors as contextual cues that are related to alcohol consumption. The intoxicating and incentive salience effects of alcohol are underpinned by circuits that converge on the nucleus accumbens that involve GABA, glutamate, endogenous opioids, and dopamine. Glutamate and dopamine also act on the basal ganglia to support the development of pathological habits. The negative emotional state that is experienced in the *withdrawal/negative affect* stage is hypothesized to involve the extended amygdala, including the nucleus accumbens. The negative emotional effects may be related to the loss of function of endogenous opioids, GABA, and dopamine and the recruitment of arousal/stress factors, such as CRF, norepinephrine, hypocretin, and dynorphin, producing a gain in stress reactivity. The extended *preoccupation/anticipation* stage in AUD that lasts long into abstinence involves compromised frontal cortical executive function and the dysregulation of substrates that mediate craving. These may be related to the dysregulation of glutamatergic projections from the frontal cortex and basolateral amygdala to the nucleus accumbens [27]. They may also be related to irreversible changes in the structure and function of the prefrontal cortex and neuronal connections that subserve circuits that link the prefrontal cortex to other parts of the brain [271, 272].

Sleep disturbances, alterations of sleep architecture, and the development of insomnia are almost ubiquitous in AUD. During the *binge/intoxication* stage, alcohol intoxication leads to a faster sleep onset, but the quality of subsequent sleep is poor relative to nights when no alcohol is consumed, with a substantial increase in wakefulness during the sleep period, especially later in the night. REM sleep is reduced early in the night, with some limited compensation later in the sleep period. Slow-wave sleep and EEG delta frequency increase early in the night following alcohol intoxication, but the normal benefits of SWS may not occur because of an increase in alpha activity that can be seen concurrently with an increase in delta (i.e., so-called alpha-delta sleep). The reduction of SOL and increase in delta activity may be related to the acute effects of alcohol on GABAergic systems that are associated with sleep regulation. The GABA receptor agonist properties of alcohol may also be at least partially responsible for the initial suppression of REM sleep.

Sleep effects in the *withdrawal/negative affect* stage are highly variable. Although there is a trend toward a decrease in SWS and some limited rebound in REM sleep when AUD individuals stop drinking, there appears to be limited recovery in sleep disturbances that are seen in AUD within the first 30 days of abstinence. The effects of withdrawal on sleep variables may also be related to the loss of alcohol as a positive allosteric modulator of $GABA_A$ receptors and the decrease in dopamine function. The overactivation of hypocretin/orexin peptides during drug withdrawal may also destabilize the boundaries between arousal sleep states that are found in acute and protracted abstinence. Other neurotransmitter and neuromodulator systems, such as norepinephrine, CRF, and cytokines, may also be involved.

The extended *preoccupation/anticipation* stage in long-term abstinent AUD individuals is associated with persistent sleep issues, including a longer sleep latency, more time awake during the night, a decrease in SWS, a decrease in delta EEG power and evoked delta activity, and an increase in REM sleep. Some of these factors, especially the reduction of spontaneous and evoked delta activity, may be related to the known, largely irreversible acceleration of brain shrinkage that is seen in AUD, especially in the frontal and prefrontal areas of the brain where delta activity is also predominant [75].

Clinically significant insomnia is highly prevalent in long-term abstinent AUD individuals and has been linked to an increase in the propensity to relapse. The dysregulation of glutamatergic systems that is observed in AUD is a likely substrate for some of the observed protracted and persistent sleep dysregulations. Several studies have shown that drugs that are used to treat AUD may also play a role in normalizing sleep in the acute withdrawal and extended abstinence periods. This is true for acamprosate, a

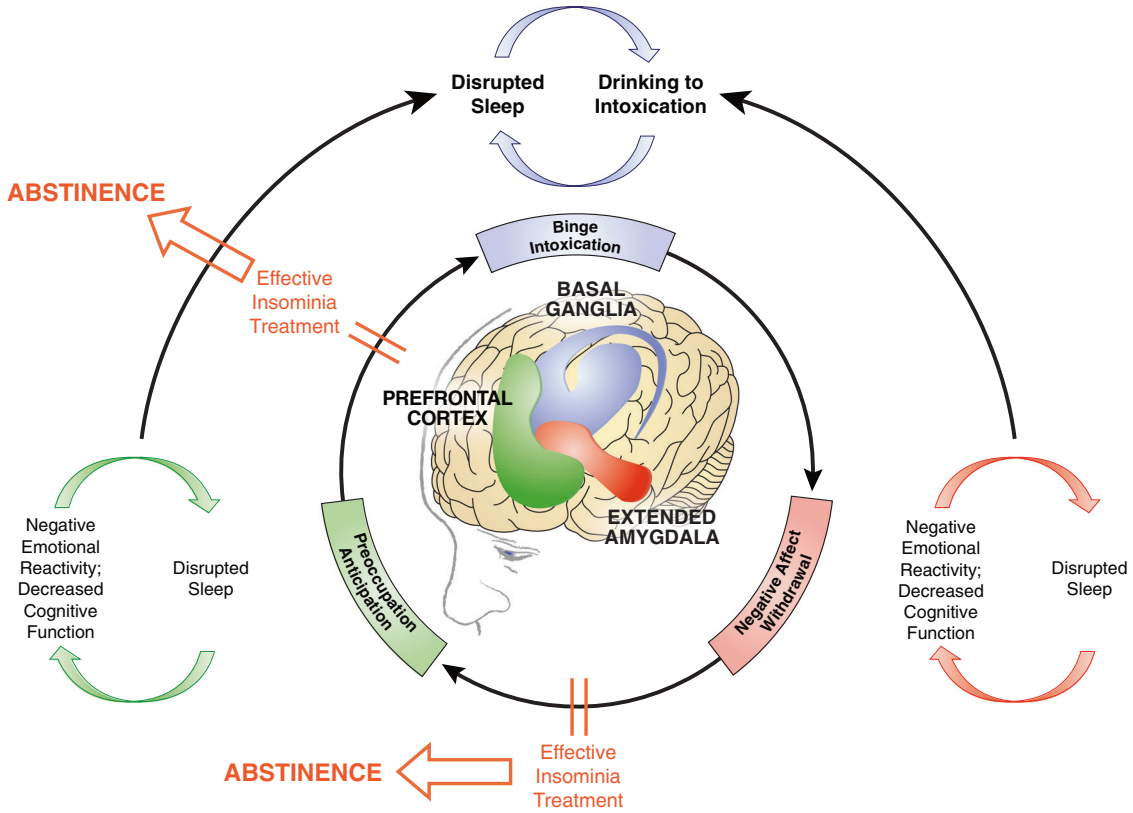

Fig. 4 Framework for how sleep dysregulation is caused by alcohol use disorder and itself causes or exacerbates alcohol use disorder. In the *binge/intoxication* stage, drinking to intoxication or binge drinking is hypothesized to disrupt sleep, and the consequent sleep disruption is hypothesized to drive further excessive alcohol drinking. In the *withdrawal/negative affect* stage, withdrawal disrupts sleep and may be a trigger for excessive drinking to provide relief from insomnia. In the *preoccupation/anticipation* stage, residual sleep dysregulation may set up relapse, particularly when paired with stress and/or alcohol-related cues. The treatment of sleep disturbances, particularly in the *withdrawal/negative affect* stage and *preoccupation/anticipation* stage, is hypothesized to help promote abstinence and treat alcohol use disorder

glutamatergic allosteric modulator, and even more so for gabapentin, a modulator of voltage-dependent neuronal Ca^{2+} channels [273]. Given the link between insomnia and relapse and the exacerbation of emotional dysregulation, fatigue, and cognitive symptoms of withdrawal that are provided by sleep disturbance, effective treatments for insomnia in the *withdrawal/negative affect* and *preoccupation/anticipation* stages could likely help lead to continued abstinence and prevent relapse.

More studies of the role of insomnia in abstinence and withdrawal are clearly warranted, especially in women. One particular aspect of such studies would be to systematically evaluate whether modulation of the brain stress systems, including the hypocretin/orexin system, has a positive impact on alcohol withdrawal and its associated sleep disturbances. The orexin/hypocretin system is composed of two neuropeptides, hypocretin-1 (orexin-A) and hypocretin-2 (orexin-B), and two excitatory G-protein coupled receptors, hypocretin-1 (orexin-1) and hypocretin-2 (orexin-2). Hypocretin-1 receptors appear to be more potent as a modulator of sleep and wakefulness [274]. The antagonism of hypocretin-1 receptors has been shown to prevent alcohol-seeking behavior in several animal models (for review, see [275]) and may directly address features in the *withdrawal/negative affect* and *preoccupation/anticipation* stages of AUD. The use of dual hypocretin receptor antagonists, such as the FDA-approved drug suvorexant, could lead to improvements in abstinence outcomes in AUD. It is an effective treatment for insomnia [276] and has shown some promise in impacting addiction in preclinical models [277]. Other brain stress systems that contribute in animal studies to negative emotional states that drive negative reinforcement in the *withdrawal/negative affect* stage may either directly or indirectly impact sleep mechanisms, including norepinephrine, glucocorticoids, CRF, and even the dynorphin-κ opioid receptor system. Finally, from a neurobiological perspective, sleep-inducing systems may buffer sleep-disrupting systems in parallel with buffers to the brain arousal stress systems, such as NPY, endocannabinoids, and oxytocin. Sleep is a modifiable behavior that may have a positive impact on abstinence in AUD and may lead to improvements in cardiovascular risk profiles.

From the perspective of translation to the clinical domain, much more work is needed to answer key questions about whether treating sleep disturbances in AUD is a key to treatment, particularly during protracted abstinence in the *preoccupation/anticipation* stage and *withdrawal/negative affect* stage (Fig. 4). Sleep pathology clearly contributes to AUD pathology, and AUD pathology contributes to sleep pathology. This type of feed-forward drive to a nonhomeostatic state fits well within an allostatic view of addiction, in which the hedonic set point resets at an abnormal, near pathological level that drives further alcohol seeking in a failed attempt to restore a normal hedonic set point in the form of misregulaton [15]. Sleep disturbances then become another part of allostatic load that drives the addiction process.

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