Alterations in circadian rhythms following alcohol use: A systematic review

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Abstract (249 words)

Increasing evidence suggest a bidirectional link between disrupted circadian rhythms and alcohol use disorders (AUD). A better understanding of these alcohol-induced changes in circadian rhythms will likely provide important therapeutic solutions. We conducted a systematic review based on the PubMed database examining biological rhythms in all stages of alcohol use: acute alcohol consumption, AUD, alcohol withdrawal, and abstinence. Different changes in circadian rhythms have been observed after a single acute alcohol intake, but also during AUD and alcohol withdrawal. Following a single acute alcohol intake, changes in biological rhythms are dose-dependent, reflected in the melatonin and cortisol secretions, and the core body temperature (CBT) rhythms. These alterations normalize the next morning and appear mostly for acute alcohol intake higher than 0.5g/kg. These alterations are more severe during AUD and persist over time. In addition, interestingly, opposite patterns of the melatonin physiological ratio between diurnal and nocturnal secretion (N/D ratio <1) have been observed during AUD and appear to be a marker of chronic daily use. During alcohol withdrawal, circadian rhythms desynchronization correlates with the severity of alcohol withdrawal symptoms and withdrawal complications such as delirium tremens. During abstinence a resynchronization of circadian rhythms of cortisol and CBT appears in most patients about one month after alcohol withdrawal. Disruption of melatonin circadian rhythms can persist after 3-12 weeks of abstinence. The circadian genetic vulnerability associated with biological rhythms alterations in alcohol use disorders increases the risk of relapses. Circadian-based interventions could play a critical role in preventing and treating AUD.

Keywords: Circadian rhythms; Alcohol; Alcohol use disorder; Melatonin; Temperature; Cortisol.

Introduction:

Alcohol is the most widely used psychoactive substance and represents a major public health concern. The total worldwide consumption of alcohol per capita for people over the age of 15 continues to increase. This consumption has increased from 5.5 liters of pure alcohol in 2005 to 6.4 liters in 2010, and has remained at 6.4 liters in 2016 (World Health Organization, 2011). 2.3 billion people are current drinkers, and among them, an estimated 237 million men and 46 million women have developed alcohol use disorders (AUD) (World Health Organization, 2011).

Alcohol, and more specifically excessive alcohol use disorder, is responsible for numerous mental and physical health problems, including alcohol-related car crashes (Behnood and Mannering, 2017) cancers (Seitz, 2017) depression (Boden and Fergusson, 2011), or sleep disorders (Chakravorty et al., 2016), etc. Most of excessive AUD affects teenagers. According to the 2016 National Survey on Drug Use and Health (NSDUH), 9% of adolescents aged 12 to 17 years reported past-30-day alcohol use (so defined as current drinkers) and 5% reported current binge drinking (Park-Lee et al., 2012). Adverse life events are associated with negative outcomes in young people, and also seem to have a positive dose-response relation with youth suicidality (both suicidal ideation and attempts) (Serafini et al., 2015). The link between alcohol use and negative life events, such as suicide, may be mediated by alterations of sleep and circadian rhythms (Benard et al., 2019, 2015)

Impacts on sleep have been reported during acute administration, alcohol abuse, dependence, continue to last during periods of abstinence and may play a role in relapse (Colrain et al., 2009). In parallel, studies have provided compelling evidence of a bidirectional link between disrupted circadian rhythms and alcohol, most of them being reported on AUD. First, it has been observed that changes in circadian rhythms also occur during acute alcohol consumption and have different effects depending on the time of administration (Gulick and Gamsby, 2018). Second, disrupted circadian rhythms may be a factor in the development of AUD. For example, The “evening” chronotype -i.e. an evening phase preference - has been associated with a higher risk of developing AUD (Gulick and Gamsby, 2018; Lemoine et al., 2013). Moreover, at a clinical level, circadian rhythms abnormalities, such as those

observed in shift workers and adolescents, have been found to increase the susceptibility to addiction (Gulick and Gamsby, 2018). Furthermore, multiple bidirectional interactions between circadian and reward-related rhythms have been supported at both the molecular and genetic levels (Banach et al., 2018; Gulick and Gamsby, 2018). On therapeutic grounds, persistent sleep disorders and circadian rhythms abnormalities are associated with an increased risk of relapse (Roth and Workshop Participants, 2009). A recent literature review has recommended for the management of AUD to include the assessment of circadian rhythms using actigraphy and, if needed, the correction of the identified abnormalities using rhythm-focused therapeutic measures (Hasler et al., 2012).

To date, no review has yet proposed a comprehensive model from alcohol-induced changes in circadian biological rhythms. We hypothesized that different chronobiological effects of alcohol may depend on the duration of the exposition to alcohol. In this context, this systematic review aims to examine biological rhythms during acute alcohol consumption, alcohol use disorder, alcohol withdrawal, and alcohol abstinence stages.

Material and methods:

Research strategy

A Systematic Literature Review was conducted in July 2018. This systematic review was reported using the PRISMA guidelines (Moher et al., 2009). To collect all relevant studies, we searched for the abstract, title, and keyword fields in the MEDLINE electronic database to identify the studies that focused on evaluating circadian rhythms in alcohol regardless of the type of alcohol use. We used the following keywords: “alcohol” and ("circadian" or "circadian rhythms").

Study selection

Searches were limited to the English language and to studies involving human participants without date restriction. We started by removing duplicates. Then, two authors (MM and PAG) reviewed the titles and abstracts of the respective identified publications in order to identify the eligible studies. The two resulting lists of articles were then compared and, in case of disagreement, the final decision as to whether the article should be included or not was made by consensus. MM and PAG selected independently and then jointly the studies from which to extract detailed information, mostly based on the full text. Where the full text was not available, the corresponding authors were contacted. If a reply was not obtained within 4 months of contacting them, the abstracts were considered in the review only if the appropriate information was included.

All papers describing research on circadian rhythms in alcohol were included. All studies describing research in alcohol and assessing any component of circadian rhythms (melatonin, cortisol, actigraphy and core body temperature) were included. Human studies focusing on cirrhosis as a potential confounding factor were excluded. Indeed, previous studies have reported aberrations in melatonin and adrenal circadian rhythms in patients with chronic liver disease due to impaired hepatic catabolism (Celinski et al., 2009; Steindl et al., 1997, 1995; Tana et al., 2018)). Studies focusing on dynamic function tests (Insulin Hypoglycemic Test, Dexamethasone Test) were also excluded.

Reviews, meta-analyses, commentaries, case reports, and articles including fewer than five subjects were excluded.

For the second step, we excluded full-text articles whether they were not off-topic (n=4) or included fewer than 5 participants (n=2) or were case reports/ short commentaries (n=1). See Figure 1 for details.

Four types of alcohol stages were reported among the selected studies: acute alcohol consumption, AUD, alcohol withdrawal, and alcohol abstinence. We have divided literature results into four main sections depending on circadian rhythms exploration: (1) melatonin, (2) core body temperature, (3) actigraphy and (4) cortisol modifications during each of the possible four stages: acute alcohol consumption, AUD, alcohol withdrawal, and alcohol abstinence. Two groups of patients were identified with AUD: patients with alcohol dependence based on the DSM-III/ DSM-IV criteria, and patients with heavy alcohol drinking (HAD) who were defined as subjects suffering from binge drinking (which is a pattern of drinking that brings blood alcohol concentration (BAC) levels to 0.08 g/dL and that typically occurs after 4 drinks for women and 5 drinks for men—in about 2 hours) over the course of five or more days in the past month, but did not meet the DSM-III and DSM-IV criteria for alcohol dependence ("Alcohol Facts and Statistics | National Institute on Alcohol Abuse and Alcoholism (NIAAA)," n.d.).

RESULTS:

1. MELATONIN SECRETION AND ALCOHOL USE:

Table 1 summarizes studies that examine the relationship between melatonin secretion and alcohol use.

1.1. MELATONIN SECRETION AND ACUTE ALCOHOL CONSUMPTION

Seven studies have evaluated salivary melatonin levels in healthy patients after an acute alcohol intake (Table 1). Two articles focused on acute low alcohol consumption (<0.5g/kg) (Danel and Touitou, 2006; Röjdmark et al., 1993), six on moderate acute alcohol consumption (0.5g/kg and <0.8g/kg) (Burgess et al., 2016; Ekman et al., 1993; Hartman et al., 2012; Röjdmark et al., 1993; Rupp et al., 2007; Swanson et al., 2016) and three on acute high alcohol consumption (≥ 0.8g/kg) (Burgess et al., 2016; Ekman et al., 1993; Hartman et al., 2012).

1.1.1. Plasmatic melatonin levels:

Seven studies have evaluated melatonin levels in healthy patients after an acute alcohol intake. No changes in melatonin levels were observed after a low acute alcohol consumption (< 0.5g/kg) (Danel and Touitou, 2006; Röjdmark et al., 1993). For moderate acute alcohol consumption (≥ 0.5g/kg and < 0,8g/kg), three studies described a decrease in salivary or plasma levels of melatonin following moderate acute alcohol intake (Ekman et al., 1993; Röjdmark et al., 1993; Rupp et al., 2007). What is worthy of note, however, is that three studies reported unchanged melatonin levels after alcohol intake and were thus not able to confirm the previous observations (Burgess et al., 2016; Swanson et al., 2016). Melatonin reduction rates varied from 15% to 41% across studies. The decrease in these melatonin rates appeared to be transient and normalized the next day (Ekman et al., 1993).

Three studies have assessed salivary or plasma melatonin levels following high acute alcohol consumption (≥ 0,8g/kg). One of these studies reported no change in melatonin levels (Burgess et al., 2016). However, Ekman et al, 1993 has reported a decrease in melatonin levels of the same range effect as those observed for moderate acute alcohol consumption but without an increased duration (Ekman et al., 1993).

As for temporal patterns of melatonin after acute consumption, delay in the onset of melatonin secretion and a slower growth rate were described in a subgroup of patients after a low acute alcohol consumption (<0,5g/kg) (Danel and Touitou, 2006). In studies assessing the effects of moderate to high acute alcohol consumption, the onset of melatonin secretion under dim light conditions, called dim light melatonin onset DMLO, in day workers (Rupp et al., 2007; Swanson et al., 2016) remained unchanged after high acute alcohol intake, similarly to diurnal rhythms and nocturnal rise of melatonin (Ekman et al., 1993). Moreover, no effect of a single dose of alcohol on circadian phase shifts to light has been reported (Burgess et al., 2016).

1.1.2. Urinary melatonin levels:

Three studies were found that evaluated the urinary excretion levels of the first melatonin metabolite 6-sulfatoxymelatonin following an acute alcohol intake at low, moderate and high levels. These studies have found no disturbance of urinary excretion of 6-sulfatoxymelatonin (Ekman et al., 1993; Hartman et al., 2012; Röjdmark et al., 1993).

1.2. MELATONIN AND ALCOHOL USE DISORDER:

Three studies have evaluated the melatonin secretion in AUD. All studies have evaluated patients with alcohol dependence (Danel et al., 2009; Murialdo et al., 1991a; Swanson et al., 2015). No study evaluating melatonin in HAD was found. One study assessed plasma levels and circadian rhythms

of melatonin (Swanson et al., 2015) and two studies investigated urinary melatonin levels in AUD (Danel et al., 2009; Murialdo et al., 1991a)

1.2.1. Plasmatic melatonin levels:

Plasma melatonin levels decreased proportionally with age in AUD (Swanson et al., 2015). Moreover, the DMLO happened earlier and the median peak melatonin amplitude decreased.

1.2.2. Urinary melatonin levels:

Two studies have evaluated urinary melatonin levels in AUD. Higher diurnal 24-hour urine melatonin levels and a disruption of the physiological ratio between diurnal and nocturnal secretion (N/D ratio <1) were reported (Danel et al., 2009; Murialdo et al., 1991a). The pattern of melatonin excretion in AUD was a reversal of its usual pattern leading to more secretion in the day as opposed to physiological night secretion in healthy individuals. In addition, positive correlations were observed between N/D ratio and the age at onset of consumption (rho = 0.874, P = 0.010) or the age at onset of AUD (rho = 0.758; P = 0.048) (Danel et al., 2009). As a consequence, patients at an earlier age at onset of consumption and at an earlier age at onset of dependence had the lowest ratio between diurnal and nocturnal secretion.

1.3. MELATONIN SECRETION AND ALCOHOL WITHDRAWAL

Three studies have evaluated melatonin secretion during alcohol withdrawal (Table 2). Two studies focused on the first days of alcohol withdrawal (Mukai et al., 1998a; Schmitz et al., 1996) and one on the end of the withdrawal period (Danel et al., 2009).

1.3.1. Plasmatic melatonin levels:

One study evaluated plasma melatonin levels on the first four days of alcohol withdrawal. The average of melatonin secretion decreased continuously throughout the withdrawal (Schmitz et al.,

1996). Five out of ten patients saw nearly no night-time melatonin secretion with peak values of less than 30 pg/mL (Schmitz et al., 1996).

Furthermore, during alcohol withdrawal, patients without delirium tremens had normal circadian variation of melatonin (Mukai et al., 1998a). Desynchronization of melatonin's circadian rhythms and a decreased amplitude in its secretion were reported only in patients with delirium tremens (Mukai et al., 1998a). These alterations in melatonin secretion were transient and did not persist beyond the first month of alcohol withdrawal (Mukai et al., 1998a).

1.3.2. Urinary melatonin levels:

One small study conducted on seven patients evaluated urinary melatonin level during alcohol withdrawal (Danel et al., 2009). During alcohol withdrawal, pattern of melatonin excretion (N/D ratio <1) tended to normalize with alcohol cessation after 15 days (in four out of seven patients) except for three patients with the highest average daily alcohol consumption (Danel et al., 2009).

1.4. MELATONIN AND ALCOHOL ABSTINENCE

Five studies evaluated melatonin secretion in patients who have been abstinent from alcohol (Table 3). All studies evaluated patients with alcohol dependence. No study evaluating melatonin in HAD was found. Three studies were conducted in patients with short-term abstinence (abstinence < 1 month) (Fonzi et al., 1994; Kühlwein et al., 2003; Murialdo et al., 1991a), and two studies were conducted in patients with a median-term abstinence approach (mean abstinence duration: 57.9 ± 19.3 days in Conroy et al, 2012; and 1 month of abstinence in Mukaï et al, 1998) (Conroy et al., 2012a; Mukai et al., 1998a).

1.4.1. Plasmatic melatonin levels:

Three studies evaluated plasma melatonin levels in patients who have been abstinent from alcohol. Two studies reported melatonin levels comparable to those of normal controls (Fonzi et al., 1994; Murialdo et al., 1991a) and one study reported decreased plasma melatonin levels during the early part of the night (Kühlwein et al., 2003).

Results on melatonin patterns during abstinence were inconsistent. Two studies revealed unchanged melatonin levels (Fonzi et al., 1994; Mukai et al., 1998a) and two studies reported abnormal melatonin secretion during alcohol abstinence (Conroy et al., 2012a; Kühlwein et al., 2003). In those studies, delay in the onset of the nocturnal plateau (Kühlwein et al., 2003) or later DMLO with a lower maximal amplitude and a slower rate of rise (Conroy et al., 2012a) were reported. These changes were both associated with sleep disturbances (Conroy et al., 2012a; Kühlwein et al., 2003). A lower phase angle difference between DLMO and the middle of the habitual sleep period were reported during alcohol abstinence (Conroy et al., 2012a) and Kulwhein et al found a correlation between nocturnal delay of melatonin and prolonged sleep latency in (Kühlwein et al., 2003).

1.4.2. Urinary melatonin levels:

One study evaluated urinary melatonin concentration in patients who have been abstinent from alcohol (Murialdo et al., 1991b). During alcohol abstinence, patients had a mean Nocturnal/Diurnal ratio of melatonin secretion similar to those of healthy controls (Murialdo et al., 1991b) .

2. CORE BODY TEMPERATURE AND ALCOHOL USE:

Table 2 summarized studies that examine the relationship between core body temperature and alcohol use.

2.1. CORE BODY TEMPERATURE AND ACUTE ALCOHOL CONSUMPTION

2.1.1. Low acute alcohol consumption:

Two studies have assessed changes in core body temperature of healthy subjects after acute low alcohol consumption (< 0,5g/kg) (Danel et al., 2001; Devaney et al., 2003). Two types of effects of acute alcohol intake on core body temperature were reported: an acute effect and a delayed effect (Devaney et al., 2003). The acute effect consisted in a decreased core body temperature in subjects. This was reported in both studies (Danel et al., 2001; Devaney et al., 2003). Such effect of alcohol on the core body temperature was described as being time-dependent in the study of Devaney et al, 2003 (Devaney et al., 2003). In this study, acute effects were reported after drinking alcohol at 1pm but not at 6pm (Devaney et al., 2003).

In the second study, such effects were not described as being time-dependent; however, an ethanol concentration of 256 mg/dl was administered intravenously on a continuous basis between 10am the first day and 12pm on the second day (Danel et al., 2001). The delayed effect featured a dampening of the core body temperature trough due to alcohol as opposed to the temperature under no consumption of alcohol(Devaney et al., 2003). This effect was reported in both studies, irrespective of the time of ingestion (Danel et al., 2001; Devaney et al., 2003).

2.1.2. Moderate / High acute alcohol consumption:

No studies have evaluated circadian rhythms changes in healthy subjects after an acute moderate or high consumption of alcohol (≥ 0,5g/kg).

2.2. CORE BODY TEMPERATURE IN ALCOHOL USE DISORDER:

No studies have evaluated changes in core body temperature in AUD.

2.3. CORE BODY TEMPERATURE AND ALCOHOL WITHDRAWAL

One study evaluated the core body temperature during alcohol withdrawal (Kodama et al., 1988). Several characteristics of circadian rhythms of the body core temperature were revealed to have changed during alcohol withdrawal. Although normal periods were observed in all patients throughout the study, an abnormal acrophase was found in many patients, especially in those with depression and alcohol dependence. On the 3rd and 4th days following alcohol withdrawal, all four patients with depression and alcohol dependence showed a phase advance of the circadian rhythm, and three out of six patients without depression and alcohol dependence exhibited an abnormal acrophase. On the 21st and 22nd days following alcohol withdrawal, a normal acrophase was observed in two out of four patients with depression and in four out of six without depression. However, the mesor and periods seem to remain unchanged during alcohol withdrawal.

2.4. CORE BODY TEMPERATURE AND ALCOHOL ABSTINENCE

One study evaluated the core body temperature during alcohol abstinence (Kodama et al., 1988). Changes in core body temperature reported during alcohol withdrawal tend to normalize after 21 days of alcohol abstinence (Kodama et al., 1988). Only an abnormal daily pattern persists during abstinence (Kodama et al., 1988).

3. CORTISOL AND ALCOHOL:

Table 3 summarizes the studies that examine the relationship between cortisol secretion and alcohol use.

3.1. CORTISOL SECRETION AND ACUTE ALCOHOL CONSUMPTION

19 studies evaluated plasma or urinary cortisol levels variations during acute consumption (Table 3). 18 studies assessed plasma cortisol variations after an acute and single alcohol intake and one study evaluated urinary cortisol levels after high acute alcohol intake.

3.1.1. Plasma Cortisol levels:

18 studies assessed plasma cortisol variations after an acute and single alcohol intake. One study evaluated plasma cortisol after low acute alcohol intake (< 0.5g/kg) (Sarkola et al., 1999), seven studies after moderate acute alcohol consumption (≥ 0.5g/kg and < 0,8g/kg) (Bellet et al., 1970; Danel and Touitou, 2006; Davis and Jeffcoate, 1983; Ekman et al., 1994; Gianoulakis et al., 1989; Sarkola et al., 1999; Waltman et al., 1993) and ten after high acute alcohol consumption (≥ 0,8g/kg) (Aguirre et al., 1995; Ekman et al., 1994; Frias et al., 2002; Ida et al., 1992; Jenkins and Connolly, 1968; Linkola et al., 1979; Mander et al., 1989; Prinz et al., 1980; M. J. Välimäki et al., 1984; Ylikahri et al., 1978)

In the literature, no changes in cortisol levels have been reported after a low acute alcohol intake (< 0.5g/kg) (Sarkola et al., 1999). In the case of moderate acute alcohol consumption (≥ 0.5g/kg and < 0,8g/kg), five studies reported unchanged cortisol levels after alcohol intake (Danel and Touitou, 2006; Davis and Jeffcoate, 1983; Ekman et al., 1994; Sarkola et al., 1999; Waltman et al., 1993). What is worthy of note, however, is that two studies described small and short-term increases in plasma levels (Bellet et al., 1970; Gianoulakis et al., 1989). Such increases were short-term (less than 120 mins) (Gianoulakis et al., 1989) and could range from 8 to 23% (Bellet et al., 1970). In the case of high acute alcohol consumption (≥ 0,8g/kg), six studies have reported an increase in plasma levels of cortisol (Ekman et al., 1994; Frias et al., 2002; Jenkins and Connolly, 1968; Mander et al., 1989; M. J. Välimäki et al., 1984; Ylikahri et al., 1978), four studies have found no change in plasma cortisol levels (Aguirre et al., 1995; Ida et al., 1992; Prinz et al., 1980; Sarkola et al., 1999), one study reported biphasic variations in plasma cortisol levels (Linkola et al., 1979). Only one study found a decreased level in cortisol following an acute alcohol intake (Ida et al., 1992).

Increases in cortisol levels after high alcohol intake were significant and sometimes reached up to 152% (M. J. Välimäki et al., 1984). They lasted between 24 hours and four days (Mander et al., 1989; M. J. Välimäki et al., 1984), and were greater in patients with higher basal alcohol consumption (Badrick et al., 2008). These variations were neither correlated with the intensity of the hangover (Ylikahri et al., 1978), nor with the blood alcohol concentration (Mander et al., 1989).

Moreover, genetic susceptibility factors associated with AUD affected plasma cortisol levels after acute alcohol intake (Gianoulakis et al., 1989; Schuckit et al., 1987). Patients with family history of AUD (Gianoulakis et al., 1989; Schuckit et al., 1987) saw a smaller increase in plasma cortisol after acute alcohol intake than in healthy controls.

No study evaluating the patterns of cortisol after low alcohol intake was found. No modification of cortisol rhythms have been reported after a single moderate alcohol intake (Danel and Touitou, 2006; Ekman et al., 1994). For single high alcohol intake, inconsistent results were found. Two studies reported no changes in circadian rhythms of serum cortisol (Ekman et al., 1994; Prinz et al., 1980). In contrast, two studies found changes featuring a decline in cortisol over the day as well as a cortisol awakening response (Frias et al., 2002; Inder et al., 1995b). Declines along diurnal rhythms were higher on the day of alcohol consumption (Inder et al., 1995b).

3.1.2. Urinary cortisol levels:

One study evaluated urinary cortisol levels after high acute alcohol intake. Urinary cortisol levels were significantly higher in the patient group with the highest alcohol acute intake (high alcohol subgroup: 35.7 g/day; low alcohol subgroup 8.0 g/day)(Thayer et al., 2006).

3.2. CORTISOL AND ALCOHOL USE DISORDER

Eight studies evaluated cortisol variations in AUD. Seven studies focused on plasma cortisol concentrations and circadian rhythms (Bertello et al., 1982; Boschloo et al., 2011; Gianoulakis et al., 1989; Mander et al., 1989; Margraf et al., 1967; Mendelson et al., 1971; Wand and Dobs, 1991)(Bertello et al., 1982; Boschloo et al., 2011; Mander et al., 1989; Margraf et al., 1967; Wand and Dobs, 1991). Three studies assessed urinary cortisol levels (Hasselbalch et al., 1982; Margraf et al., 1967; Wand and Dobs, 1991).

3.2.1. Plasma Cortisol levels:

With regard to plasma cortisol levels, four studies evaluated plasma cortisol levels in patients with alcohol dependence (Bertello et al., 1982; Boschloo et al., 2011; Margraf et al., 1967; Mendelson et al., 1971; Wand and Dobs, 1991) and three assessed patients suffering from HAD (Boschloo et al., 2011; Gianoulakis et al., 2003; Mander et al., 1989).

In studies that evaluated plasma cortisol levels in patients with alcohol dependence, discordant results were reported: two studies found increased plasma cortisol levels (Margraf et al., 1967; Mendelson et al., 1971) and one study reported levels that were similar to those of the controls (Wand and Dobs, 1991). Furthermore circadian profiles of plasma cortisol levels in patients with alcohol dependence were similar to those in healthy controls (Bertello et al., 1982). Finally, a correlation between an increase in serum cortisol levels and a progressive increase in blood alcohol levels - indicating a general dose-response relationship - was reported (Mendelson et al., 1971). No association between a lifetime diagnosis of alcohol dependence and cortisol levels was found (Boschloo et al., 2011).

In studies that evaluated plasma cortisol levels in patients with HAD, higher basal cortisol levels were described in heavy drinkers than in moderate drinkers, non-drinkers or abstinent AUD (Boschloo et al., 2011; Gianoulakis et al., 2003; Mander et al., 1989). No correlation between blood alcohol

concentration and subsequent changes over the first 24-hour period in cortisol levels was reported (Gianoulakis et al., 2003; Mander et al., 1989).

3.2.2. Urinary cortisol levels:

Three studies evaluated urinary cortisol levels in AUD. Two studies focused on patients with alcohol dependence and one study assessed HAD. Discordant results were reported in the literature with respect to plasma cortisol urinary levels in alcohol dependent patients. One study found normal basal urinary cortisol excretion in AUD (Margraf et al., 1967) and one study reported a two-fold higher rate of urinary free cortisol levels over the first 24-hour period (Wand and Dobs, 1991). Normal basal urinary cortisol excretion were found in HAD (Hasselbalch et al., 1982)

3.3. CORTISOL AND ALCOHOL WITHDRAWAL

Fifteen studies evaluated plasma cortisol variations during alcohol withdrawal. Fourteen studies assessed changes in plasma cortisol levels, five studies evaluated changes in circadian rhythms of plasma cortisol and two studies examined changes in urinary cortisol levels (Table 3).

3.3.1. Plasma Cortisol levels:

Twelve studies reported increased plasma cortisol levels during the first few days of withdrawal (Adinoff et al., 1991; Bannan et al., 1984; Fonzi et al., 1994; Heinz et al., 1995; Iranmanesh et al., 1989; Mander et al., 1989; Merry and Marks, 1972; Mukai et al., 1998b; Targum et al., 1982; von Bardeleben et al., 1989; Willenbring et al., 1984). These changes in cortisol plasma levels appeared to be related to the severity of alcohol withdrawal symptoms in two studies (Adinoff et al., 1991; Mukai et al., 1998a).. A progressive decrease in plasma cortisol levels was observed within the first days of abstinence in two studies (Mander et al., 1989; Targum et al., 1982). Finally, a normalization of plasma

cortisol levels was described in seven studies and can be observed as early as within the first week of abstinence (Adinoff et al., 1991, 1990; Fonzi et al., 1994; Heinz et al., 1995; Iranmanesh et al., 1989; M. J. Välimäki et al., 1984; von Bardeleben et al., 1989). Of note, two studies reported no changes in plasma cortisol levels during alcohol withdrawal (Costa et al., 1996; Targum et al., 1982).

Besides, changes in cortisol circadian rhythms were reported during alcohol withdrawal (Adinoff et al., 1991; Fonzi et al., 1994; Iranmanesh et al., 1989; Mukai et al., 1998b; M. Välimäki et al., 1984) and featured the following: the absence of diurnal rhythms (M. Välimäki et al., 1984), a delayed circadian acrophase (Fonzi et al., 1994; Iranmanesh et al., 1989), an increased amplitude of circadian cortisol rhythms (Iranmanesh et al., 1989) or shorter cycle length (Adinoff et al., 1991). These changes coincided with peak withdrawal symptoms (Adinoff et al., 1991) or with delirium tremens (Mukai et al., 1998a). A normalization of the cortisol rhythms was reported during the period of withdrawal in three studies and was observed after a period ranging from 1 week to 39 days of withdrawal depending on the studies (Iranmanesh et al., 1989; Mukai et al., 1998b; M. Välimäki et al., 1984).

3.3.2. ***Urinary cortisol levels:***

Two studies assessed urinary cortisol levels during alcohol withdrawal and reported contradictory results. Willenbring et al, 1984 reported a high basal 24-hour urinary cortisol levels during the first days of alcohol withdrawal, and a significant reduction after 3 weeks of abstinence (Willenbring et al., 1984). In contrast, no changes in urinary cortisol levels during a 15-day alcohol withdrawal were found in the study by Valimaki et al, 1984 (M. Välimäki et al., 1984).

3.4. CORTISOL SECRETION AND ALCOHOL ABSTINENCE

3.4.1. Plasma Cortisol levels:

Eight studies assessed plasma cortisol levels and changes in circadian rhythms in patients abstinent from AUD for more than 15 days. Salivary or blood cortisol samples were collected in the morning in four studies (Bernardy et al., 1996; Inder et al., 1995a; Junghanns et al., 2007; Lovallo et al., 2000), in the afternoon in two studies (Junghanns et al., 2003; von Bardeleben et al., 1989), in the evening in one study (Lovallo et al., 2000) and during the night in one study (Loosen et al., 1991).

All studies conducted on patients with an average abstinence duration of one month revealed plasma cortisol levels that are similar to those in healthy controls (Adinoff et al., 1990; Bernardy et al., 1996; Inder et al., 1995a; Junghanns et al., 2003; Loosen et al., 1991; Lovallo et al., 2000; von Bardeleben et al., 1989).

Discordant results were reported by studies in patients with long-term abstinence from alcohol, going from no differences at all to higher cortisol levels. Indeed, the study conducted by Adinoff et al, 1990 reported similar plasma cortisol levels in patients with long-term and short-term abstinence, while Junghans et al, 2007 described a stronger cortisol awakening response in long-term abstinent groups than in short-term abstinent groups (Adinoff et al., 1990; Junghanns et al., 2007).

In addition, circadian rhythms of plasma cortisol in patients abstinent from alcohol were similar to those in control subjects (Loosen et al., 1991; Lovallo et al., 2000).

3.4.2. *Urinary cortisol levels:*

In the literature, no studies evaluating urinary cortisol levels in patients abstinent from AUD were found.

4. ACTIGRAPHY AND ALCOHOL:

Only one study assessed phase markers and did not observe differences at wake-up time and bedtime between AUD patients and controls (Conroy et al., 2012b) .

Other actigraphy studies assessing patients during acute alcohol consumption, dependence, withdrawal or abstinence focused only on sleep markers and not circadian rhythms, including total sleep time (TST), sleep efficiency (SE), time in bed (TIB), sleep latency (SOL), activity score (AS), wake after sleep onset (WASO), fragmentation (%), and sleep percentage (Geoghegan et al., 2012; Smith et al., 2014; Swanson et al., 2016, 2015).

5. DISCUSSION

This systematic study highlights different changes in circadian rhythms (melatonin, core body temperature, cortisol, and actigraphy) following an acute alcohol intake, AUD, alcohol withdrawal, and alcohol abstinence.

Following a single acute alcohol intake, changes in circadian rhythms are dose-dependent. After a low acute alcohol intake (< 0.5g/kg), only the amplitude of the circadian temperature rhythms is reduced with higher temperatures at night and lower temperatures in day time. Plasmatic levels, urinary excretion and circadian variations of melatonin and cortisol circadian rhythms remain unchanged.

Moderate (≥0.5g/kg and <0,8g/kg), and high acute alcohol intake (≥ 0,8g/kg) are both associated with changes in plasma cortisol and melatonin levels (increased plasmatic cortisol levels, decreased plasmatic melatonin levels) and in cortisol excretion (increased urinary cortisol levels). No change in melatonin excretion occurs. Cortisol levels are altered in a linear dose-dependent manner (low dose and short-term variations of cortisol levels are reported after moderate acute alcohol intake whereas, after a high acute alcohol intake, alterations of cortisol levels are larger and last longer). Decrease in melatonin levels are nonlinear: variations reported after a high acute alcohol intake are longer but have the same range of effects than those after moderate acute alcohol intake. No studies evaluate core body temperature changes in healthy subjects after an acute moderate or high alcohol consumption (≥0,5g/kg).

Changes in circadian variations of cortisol are only reported after high alcohol intake, whereas those in core body temperature are reported after a low dose of alcohol intake. No changes in circadian variations of melatonin have been reported after alcohol intake except in one study with a very small sample (11 patients). Circadian phase shifts to light is not modified by a single dose of alcohol.

In alcohol use disorder, studies mainly assessed patients with alcohol dependence. Both plasma and urinary levels of cortisol and melatonin are altered in alcohol dependence. Plasma cortisol levels are increased but in contrast to the studies evaluating cortisol after acute alcohol intake, the dose-effect relationship is not always reported and circadian profiles of plasma cortisol do not change. This lack of change could be a marker of ethanol tolerance. Consistent results are reported in a previous preclinical study on zebrafish reports. In this study, acute ethanol administration was associated with increased cortisol levels in ethanol naïve zebrafish exposed to 1.00% v/v ethanol, but with an attenuated effect in zebrafish that were chronically treated with ethanol (Tran et al., 2015). Moreover in patients with alcohol use disorder, the onset of melatonin secretion in dim light condition is earlier, plasma melatonin levels decrease at night, and are associated with an opposite pattern of physiological ratio between diurnal and nocturnal secretion (N/D ratio <1). Interestingly, these ratio alterations in melatonin secretions are corrected during alcohol abstinence and are not observed during acute alcohol intake. So the reverse N/D melatonin ratio seems to be specifically related to alcohol use disorder(Murialdo et al., 1991a) and could be a marker of alcohol dependence or impregnation (Danel et al., 2009).

As for HAD, only few studies were available, and available studies only assessed cortisol. During HAD, plasma cortisol levels increase -unexpectedly with no correlations with blood alcohol concentration- and basal urinary cortisol excretion do not change. Changes in plasma cortisol levels are transient and return to normal during abstinence. These changes appear as an intermediate between more severe changes in patients with alcohol dependence and normal profiles of cortisol levels in healthy controls. Therefore a continuum may exist of circadian rhythms alterations induced by alcohol going from healthy individuals, to HAD, and alcohol dependence.

During alcohol withdrawal, nocturnal melatonin plasma levels decrease, cortisol plasma levels increase, and an advanced phase of circadian rhythm in core body temperature is reported. Changes in cortisol and melatonin levels are correlated with the severity of alcohol withdrawal symptoms and with withdrawal complications, including delirium tremens. As a result, circadian rhythms desynchronization appears to be a marker of the severity of alcohol withdrawal symptoms. Urinary excretion of melatonin and cortisol tends to normalize as the alcohol withdrawal progress. During the period of abstinence from alcohol, all circadian rhythms are resynchronized within about 2 to 3 weeks of abstinence except for melatonin levels which may remain disrupted after 3 to 12 weeks of abstinence (Conroy et al., 2012a; Kühlwein et al., 2003).

Figures 2 and 3 propose a summary of the possible effects of alcohol use on circadian rhythms. Of note, some of these effects may not exist all together in a single patient.

Circadian rhythms and sleep homeostasis are closely linked (Hubbard et al., 2013). These circadian alterations and abnormal secretions are in line with sleep disturbances reported by patients with alcohol dependence and abstinence (Kolla et al., 2014). Indeed, melatonin is a nocturnal hormone involved in sleep regulation, like the core body temperature. Therefore, melatonin disturbances and others biological alterations may have an impact on the development and maintenance of sleep, and on circadian rhythms alterations during alcohol use disorders. In addition, several studies have highlighted that changes in circadian rhythms during an acute alcohol intake were modulated by a family history of alcohol dependence, therefore highlighting a possible shared genetic linkage between alcohol-related behaviors and circadian genes (Gianoulakis et al., 1989; Schuckit et al., 1987). Other clinical and preclinical genetic studies reinforced this hypothesis. Indeed, genetic variations (single nucleotide polymorphisms or mutations) in *CLOCK, ARNTL gene, PER2 or PER3 genes* have been associated with AUD in humans (Banach et al., 2018). Moreover, alterations of circadian phenotypes such as shorter wheel-running or free-running periods (Hofstetter et al., 2003; McCulley et al., 2013; Rosenwasser et al., 2005) and less coherent activity rhythms across lighting conditions have been

reported in mice with high-alcohol-preferring (McCulley et al., 2013). These results suggest that genetic ethanol preference is associated with abnormal circadian rhythms. Such influence of circadian genes on drug-induced behaviors may be mediated through the mesolimbic dopaminergic system (McClung, 2007). Melatonin could influence drug sensitization and preference through modulation of the diurnal rhythms in dopamine transmission (McClung, 2007). Recent studies have found that, circadian rhythms In patients with cancer are a correlate of quality of life and can be a predictor of survival (Hoogland et al., 2019; Innominato et al., 2009). More generally, the alteration of these processes can result in a variety of sleep disorders or sleep disturbances in human beings (Pickering et al., 2018). In the context of alcohol treatment, symptoms of insomnia have been shown to precede and predict a relapse into alcohol use (Brower et al., 2001; Foster and Peters, 1999). Targeted interventions on circadian rhythms in abstinent patients from alcohol could enhance sustained abstinence and need to be developed. Figure 4 summarizes the genetic vulnerability and biological rhythms alterations during alcohol use disorder that may persist after withdrawal and could then lead to relapses (Figure 4).

Consequently, a bidirectional relationship may exist between disruptions in circadian rhythms and alcohol addiction vulnerability. Therapies targeting disruptions in circadian rhythms should be proposed in people with high risk of alcohol dependence, or in people who are abstinent from alcohol to help them maintain this state (Figure 3). Indeed, several preclinical trials have underlined the importance of the use of melatonin in managing addictions. For instance, the administration of melatonin at the end of the active cycle in rats caused a clear phase advance in the diurnal drinking pattern when compared to the control vehicle-treated group, and a reduced frequency of approaches to alcohol bottles (Vengeliene et al., 2015). In contrast, melatonin given at the onset of the light phase had no effect on the circadian phase and very small effects on alcohol consumption (Vengeliene et al., 2015). In addition, other preclinical studies have highlighted the ability of melatonin, or melatonin

receptor agonists, to reverse the development of tolerance and dependence to morphine (Raghavendra and Kulkarni, 1999).

It is important to recognize that there are limitations to the existing scientific literature. First, methodologies differ between studies, including variations in timeframe of blood, salivary and urinary samples, diverse light conditions that may impact circadian rhythms, inhomogeneity of the population (clinical and healthy populations) whose nutritional states, liver functions, and underlying psychiatric disorders such as depression differ from each other. Moreover, most of the studies were carried out on small population samples, which therefore limits their statistical power and interpretation.

6. CONCLUSION:

Severe alterations in biological rhythms have been observed during acute or chronic alcohol consumptions, with changes in the core body temperature and secretions of melatonin and cortisol. Abnormalities in the secretion of melatonin exist even during the period of alcohol abstinence. The withdrawal phase is associated with numerous abnormalities in circadian rhythms that tend to normalize within 1 month. Further studies need to be conducted to better understand how circadian disturbances contribute to the initiation of, and/or relapse into, alcohol use disorders; including the consideration of possible dose-relation effects and the duration of alcohol consumption. Circadian-based interventions (such as bright light therapy or melatonin treatment) could play a critical role in preventing and treating alcohol use disorders.

7. CAPTIONS:

-Table 1: Studies examining Melatonin secretion and acute alcohol consumption, dependence, withdrawal and abstinence-
Caption: ACU: Studies on acute alcohol consumption; ABS: Studies on patients abstinent from alcohol; DEP: Studies on patients with alcohol use disorder; WITH: Studies on patients during alcohol withdrawal; AUD: patients with alcohol use disorder; HC: healthy control; AUC: area under curve; DT: delirium tremens; SOL: sleep latency

- Table 2: Studies examining Body Core Temperature (CBT) and acute alcohol consumption, dependence, withdrawal and abstinence-
Caption: AUD: Patients with alcohol use disorder; CBT: Core body temperature;

-Table 3: Studies examining Cortisol secretion and acute alcohol consumption, dependence, withdrawal and abstinence-
Caption: ADSD: alcohol and stimulant dependant; AUD: patients with alcohol use disorder; DT: delirium tremens; HC: healty control; OC +: oral contraceptives users; OC-: oral contraceptives nonusers

-Figure 1 : Study flow diagram (PRISMA flow chart)

-Figure 2: Global effects of alcohol on circadian rhythms-
Caption: Nal: Normal

-Figure 3: The vicious cycle of circadian rhythms alterations in alcohol use disorder –

--Figure 4: Circadian rhythms in alcohol use disorder-
Caption: CBT: core body temperature

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Authors contribution :

MM and PAG : were responsible for the study concept and design, studies selection, data analysis and interpretation of findings
MM : drafted the manuscript
PAG and BM : provided critical revision of the manuscript for important intellectual content
All authors critically reviewed content and approved final version for publication.

8. Bibliographie

Adinoff, B., Martin, P.R., Bone, G.H., Eckardt, M.J., Roehrich, L., George, D.T., Moss, H.B., Eskay, R., Linnoila, M., Gold, P.W., 1990. Hypothalamic-pituitary-adrenal axis functioning and cerebrospinal fluid corticotropin releasing hormone and corticotropin levels in alcoholics after recent and long-term abstinence. Arch. Gen. Psychiatry 47, 325–330.
Adinoff, B., Risher-Flowers, D., Jong, J.D., Ravitz, B., Bone, G.H.A., Nutt, D.J., Roehrich, L., Martin, P.R., Linnoila, M., 1991. Disturbances of hypothalamic-pituitary-adrenal axis functioning during ethanol withdrawal in six men. Am. J. Psychiatry 148, 1023–1025.
Aguirre, J.C., del Arbol, J.L., Rico, J., Raya, J., Ruiz-Requena, M.E., 1995. Effect of acute alcohol intoxication on the opioid system in humans. Alcohol Fayettev. N 12, 559–562.
Alcohol Facts and Statistics | National Institute on Alcohol Abuse and Alcoholism (NIAAA) [WWW Document], n.d. URL https://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/alcohol-facts-and-statistics (accessed 4.9.19).
Badrick, E., Bobak, M., Britton, A., Kirschbaum, C., Marmot, M., Kumari, M., 2008. The relationship between alcohol consumption and cortisol secretion in an aging cohort. J. Clin. Endocrinol. Metab. 93, 750–757. https://doi.org/10.1210/jc.2007-0737
Banach, E., Pawlak, J., Kapelski, P., Szczepankiewicz, A., Rajewska-Rager, A., Skibinska, M., Czerski, P., Twarowska-Hauser, J., Dmitrzak-Weglarz, M., 2018. Clock genes polymorphisms in male bipolar patients with comorbid alcohol abuse. J. Affect. Disord. 241, 142–146. https://doi.org/10.1016/j.jad.2018.07.080
Bannan, L.T., Potter, J.F., Beevers, D.G., Saunders, J.B., Walters, J.R., Ingram, M.C., 1984. Effect of alcohol withdrawal on blood pressure, plasma renin activity, aldosterone, cortisol and dopamine beta-hydroxylase. Clin. Sci. Lond. Engl. 1979 66, 659–663.
Behnood, A., Mannering, F.L., 2017. The effects of drug and alcohol consumption on driver injury severities in single-vehicle crashes. Traffic Inj. Prev. 18, 456–462. https://doi.org/10.1080/15389588.2016.1262540
Bellet, S., Roman, L., DeCastro, O., Herrera, M., 1970. Effect of acute ethanol intake on plasma 11 hydroxycorticosteroid levels. Metabolism. 19, 664–667.
Benard, V., Etain, B., Vaiva, G., Boudebesse, C., Yeim, S., Benizri, C., Brochard, H., Bellivier, F., Geoffroy, P.A., 2019. Sleep and circadian rhythms as possible trait markers of suicide attempt in bipolar disorders: An actigraphy study. J. Affect. Disord. 244, 1–8. https://doi.org/10.1016/j.jad.2018.09.054
Benard, V., Geoffroy, P.A., Bellivier, F., 2015. [Seasons, circadian rhythms, sleep and suicidal behaviors vulnerability]. L'Encephale 41, S29-37. https://doi.org/10.1016/S0013-7006(15)30004-X

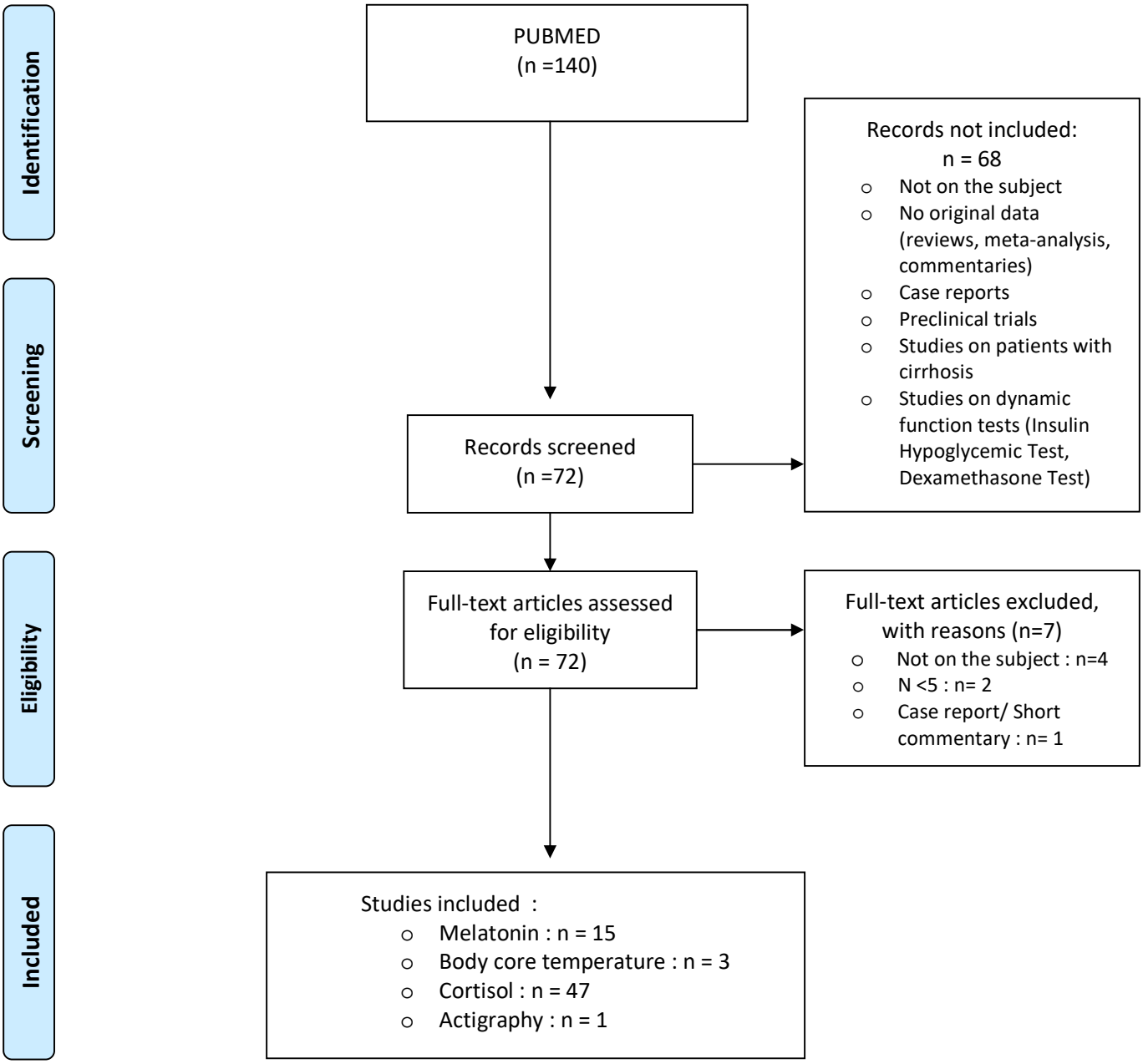
Bernardy, N.C., King, A.C., Parsons, O.A., Lovallo, W.R., 1996. Altered cortisol response in sober alcoholics: an examination of contributing factors. Alcohol Fayettev. N 13, 493–498.
Bertello, P., Agrimonti, F., Gurioli, L., Frairia, R., Fornaro, D., Angeli, A., 1982. Circadian patterns of plasma cortisol and testosterone in chronic male alcoholics. Alcohol. Clin. Exp. Res. 6, 475–481.
Boden, J.M., Fergusson, D.M., 2011. Alcohol and depression. Addict. Abingdon Engl. 106, 906–914. https://doi.org/10.1111/j.1360-0443.2010.03351.x
Boschloo, L., Vogelzangs, N., Licht, C.M.M., Vreeburg, S.A., Smit, J.H., van den Brink, W., Veltman, D.J., de Geus, E.J.C., Beekman, A.T.F., Penninx, B.W.J.H., 2011. Heavy alcohol use, rather than alcohol dependence, is associated with dysregulation of the hypothalamic-pituitary-adrenal axis and the autonomic nervous system. Drug Alcohol Depend. 116, 170–176. https://doi.org/10.1016/j.drugalcdep.2010.12.006
Brower, K.J., Aldrich, M.S., Robinson, E.A., Zucker, R.A., Greden, J.F., 2001. Insomnia, self-medication, and relapse to alcoholism. Am. J. Psychiatry 158, 399–404. https://doi.org/10.1176/appi.ajp.158.3.399
Burgess, H.J., Rizvydeen, M., Fogg, L.F., Keshavarzian, A., 2016. A single dose of alcohol does not meaningfully alter circadian phase advances and phase delays to light in humans. Am. J. Physiol. Regul. Integr. Comp. Physiol. 310, R759-765. https://doi.org/10.1152/ajpregu.00001.2016
Celinski, K., Konturek, P.C., Slomka, M., Cichoz-Lach, H., Gonciarz, M., Bielanski, W., Reiter, R.J., Konturek, S.J., 2009. Altered basal and postprandial plasma melatonin, gastrin, ghrelin, leptin and insulin in patients with liver cirrhosis and portal hypertension without and with oral administration of melatonin or tryptophan. J. Pineal Res. 46, 408–414. https://doi.org/10.1111/j.1600-079X.2009.00677.x
Chakravorty, S., Chaudhary, N.S., Brower, K.J., 2016. Alcohol Dependence and Its Relationship With Insomnia and Other Sleep Disorders. Alcohol. Clin. Exp. Res. 40, 2271–2282. https://doi.org/10.1111/acer.13217
Colrain, I.M., Turlington, S., Baker, F.C., 2009. Impact of alcoholism on sleep architecture and EEG power spectra in men and women. Sleep 32, 1341–1352.
Conroy, D.A., Hairston, I.S., Arnedt, J.T., Hoffmann, R.F., Armitage, R., Brower, K.J., 2012a. Dim light melatonin onset in alcohol-dependent men and women compared with healthy controls. Chronobiol. Int. 29, 35–42. https://doi.org/10.3109/07420528.2011.636852
Conroy, D.A., Hairston, I.S., Arnedt, J.T., Hoffmann, R.F., Armitage, R., Brower, K.J., 2012b. Dim light melatonin onset in alcohol-dependent men and women compared with healthy controls. Chronobiol. Int. 29, 35–42. https://doi.org/10.3109/07420528.2011.636852
Costa, A., Bono, G., Martignoni, E., Merlo, P., Sances, G., Nappi, G., 1996. An assessment of hypothalamo-pituitary-adrenal axis functioning in non-depressed, early abstinent alcoholics. Psychoneuroendocrinology 21, 263–275.
Danel, T., Cottencin, O., Tisserand, L., Touitou, Y., 2009. Inversion of melatonin circadian rhythm in chronic alcoholic patients during withdrawal: preliminary study on seven patients. Alcohol Alcohol. Oxf. Oxfs. 44, 42–45. https://doi.org/10.1093/alcalc/agn091
Danel, T., Libersa, C., Touitou, Y., 2001. The effect of alcohol consumption on the circadian control of human core body temperature is time dependent. Am. J. Physiol. Regul. Integr. Comp. Physiol. 281, R52-55. https://doi.org/10.1152/ajpregu.2001.281.1.R52
Danel, T., Touitou, Y., 2006. Alcohol consumption does not affect melatonin circadian synchronization in healthy men. Alcohol Alcohol. Oxf. Oxfs. 41, 386–390. https://doi.org/10.1093/alcalc/agl036
Davis, J.R., Jeffcoate, W.J., 1983. Lack of effect of ethanol on plasma cortisol in man. Clin. Endocrinol. (Oxf.) 19, 461–466.
Devaney, M., Graham, D., Greeley, J., 2003. Circadian variation of the acute and delayed response to alcohol: investigation of core body temperature variations in humans. Pharmacol. Biochem. Behav. 75, 881–887.
Ekman, A.C., Leppäluoto, J., Huttunen, P., Aranko, K., Vakkuri, O., 1993. Ethanol inhibits melatonin secretion in healthy volunteers in a dose-dependent randomized double blind cross-over study. J.

Clin. Endocrinol. Metab. 77, 780–783. https://doi.org/10.1210/jcem.77.3.8370699
Ekman, A.C., Vakkuri, O., Vuolteenaho, O., Leppäluoto, J., 1994. Delayed pro-opiomelanocortin activation after ethanol intake in man. Alcohol. Clin. Exp. Res. 18, 1226–1229.
Fonzi, S., Solinas, G.P., Costelli, P., Parodi, C., Murialdo, G., Bo, P., Albergati, A., Montalbetti, L., Savoldi, F., Polleri, A., 1994. Melatonin and cortisol circadian secretion during ethanol withdrawal in chronic alcoholics. Chronobiologia 21, 109–112.
Foster, J.H., Peters, T.J., 1999. Impaired sleep in alcohol misusers and dependent alcoholics and the impact upon outcome. Alcohol. Clin. Exp. Res. 23, 1044–1051.
Frias, J., Torres, J.M., Miranda, M.T., Ruiz, E., Ortega, E., 2002. EFFECTS OF ACUTE ALCOHOL INTOXICATION ON PITUITARY–GONADAL AXIS HORMONES, PITUITARY–ADRENAL AXIS HORMONES, β-ENDORPHIN AND PROLACTIN IN HUMAN ADULTS OF BOTH SEXES. Alcohol Alcohol 37, 169–173. https://doi.org/10.1093/alcalc/37.2.169
Geoghegan, P., O'Donovan, M.T., Lawlor, B.A., 2012. Investigation of the effects of alcohol on sleep using actigraphy. Alcohol Alcohol. Oxf. Oxfs. 47, 538–544. https://doi.org/10.1093/alcalc/ags054
Gianoulakis, C., Béliveau, D., Angelogianni, P., Meaney, M., Thavundayil, J., Tawar, V., Dumas, M., 1989. Different pituitary beta-endorphin and adrenal cortisol response to ethanol in individuals with high and low risk for future development of alcoholism. Life Sci. 45, 1097–1109.
Gianoulakis, C., Dai, X., Brown, T., 2003. Effect of chronic alcohol consumption on the activity of the hypothalamic-pituitary-adrenal axis and pituitary beta-endorphin as a function of alcohol intake, age, and gender. Alcohol. Clin. Exp. Res. 27, 410–423.
https://doi.org/10.1097/01.ALC.0000056614.96137.B8
Gulick, D., Gamsby, J.J., 2018. Racing the clock: The role of circadian rhythmicity in addiction across the lifespan. Pharmacol. Ther. 188, 124–139. https://doi.org/10.1016/j.pharmthera.2018.03.003
Hartman, T.J., Mahabir, S., Baer, D.J., Stevens, R.G., Albert, P.S., Dorgan, J.F., Kesner, J.S., Meadows, J.W., Shields, R., Taylor, P.R., 2012. Moderate alcohol consumption and 24-hour urinary levels of melatonin in postmenopausal women. J. Clin. Endocrinol. Metab. 97, E65-68.
https://doi.org/10.1210/jc.2011-1904
Hasler, B.P., Smith, L.J., Cousins, J.C., Bootzin, R.R., 2012. Circadian Rhythms, Sleep, and Substance Abuse. Sleep Med. Rev. 16, 67–81. https://doi.org/10.1016/j.smrv.2011.03.004
Hasselbalch, H., Selmer, J., Sestoft, L., Kehlet, H., 1982. Hypothalamic-pituitary-adrenocortical function in chronic alcoholism. Clin. Endocrinol. (Oxf.) 16, 73–76.
Heinz, A., Rommelspacher, H., Gräf, K.J., Kürten, I., Otto, M., Baumgartner, A., 1995. Hypothalamic-pituitary-gonadal axis, prolactin, and cortisol in alcoholics during withdrawal and after three weeks of abstinence: comparison with healthy control subjects. Psychiatry Res. 56, 81–95.
Hofstetter, J.R., Grahame, N.J., Mayeda, A.R., 2003. Circadian activity rhythms in high-alcohol-preferring and low-alcohol-preferring mice. Alcohol 30, 81–85. https://doi.org/10.1016/S0741-8329(03)00095-8
Hoogland, A.I., Bulls, H.W., Gonzalez, B.D., Small, B.J., Liu, L., Pidala, J., Jim, H.S.L., Mishra, A., 2019. Circadian rhythmicity as a predictor of quality of life in allogeneic hematopoietic cell transplant patients. J. Pain Symptom Manage. https://doi.org/10.1016/j.jpainsymman.2019.01.015
Hubbard, J., Ruppert, E., Gropp, C.-M., Bourgin, P., 2013. Non-circadian direct effects of light on sleep and alertness: lessons from transgenic mouse models. Sleep Med. Rev. 17, 445–452.
https://doi.org/10.1016/j.smrv.2012.12.004
Ida, Y., Tsujimaru, S., Nakamaura, K., Shirao, I., Mukasa, H., Egami, H., Nakazawa, Y., 1992. Effects of acute and repeated alcohol ingestion on hypothalamic-pituitary-gonadal and hypothalamic-pituitary-adrenal functioning in normal males. Drug Alcohol Depend. 31, 57–64.
Inder, W.J., Joyce, P.R., Ellis, M.J., Evans, M.J., Livesey, J.H., Donald, R.A., 1995a. The effects of alcoholism on the hypothalamic-pituitary-adrenal axis: interaction with endogenous opioid peptides. Clin. Endocrinol. (Oxf.) 43, 283–290.
Inder, W.J., Joyce, P.R., Wells, J.E., Evans, M.J., Ellis, M.J., Mattioli, L., Donald, R.A., 1995b. The acute effects of oral ethanol on the hypothalamic-pituitary-adrenal axis in normal human subjects. Clin. Endocrinol. (Oxf.) 42, 65–71.

Innominato, P.F., Focan, C., Gorlia, T., Moreau, T., Garufi, C., Waterhouse, J., Giacchetti, S., Coudert, B., Iacobelli, S., Genet, D., Tampellini, M., Chollet, P., Lentz, M.-A., Mormont, M.-C., Lévi, F., Bjarnason, G.A., Chronotherapy Group of the European Organization for Research and Treament of Cancer, 2009. Circadian rhythm in rest and activity: a biological correlate of quality of life and a predictor of survival in patients with metastatic colorectal cancer. Cancer Res. 69, 4700–4707. https://doi.org/10.1158/0008-5472.CAN-08-4747
Iranmanesh, A., Veldhuis, J.D., Johnson, M.L., Lizarralde, G., 1989. 24-Hour Pulsatile and Orcadian Patterns of Cortisol Secretion in Alcoholic Men. J. Androl. 10, 54–63. https://doi.org/10.1002/j.1939-4640.1989.tb00062.x
Jenkins, J.S., Connolly, J., 1968. Adrenocortical response to ethanol in man. Br. Med. J. 2, 804–805.
Junghanns, K., Backhaus, J., Tietz, U., Lange, W., Bernzen, J., Wetterling, T., Rink, L., Driessen, M., 2003. Impaired serum cortisol stress response is a predictor of early relapse. Alcohol Alcohol. Oxf. Oxfs. 38, 189–193.
Junghanns, K., Horbach, R., Ehrenthal, D., Blank, S., Backhaus, J., 2007. Cortisol awakening response in abstinent alcohol-dependent patients as a marker of HPA-axis dysfunction. Psychoneuroendocrinology 32, 1133–1137. https://doi.org/10.1016/j.psyneuen.2007.06.012
Kodama, H., Nakazawa, Y., Kotorii, T., Nonaka, K., Inanaga, K., Ohshima, M., Tokoyama, T., 1988. Biorhythm of core temperature in depressive and non-depressive alcoholics. Drug Alcohol Depend. 21, 1–6.
Kolla, B.P., Schneekloth, T., Biernacka, J., Mansukhani, M., Geske, J., Karpyak, V., Hall-Flavin, D., Louikianova, L., Frye, M.A., 2014. The course of sleep disturbances in early alcohol recovery: an observational cohort study. Am. J. Addict. 23, 21–26. https://doi.org/10.1111/j.1521-0391.2013.12056.x
Kühlwein, E., Hauger, R.L., Irwin, M.R., 2003. Abnormal nocturnal melatonin secretion and disordered sleep in abstinent alcoholics. Biol. Psychiatry 54, 1437–1443.
Lemoine, P., Zawieja, P., Ohayon, M.M., 2013. Associations between morningness/eveningness and psychopathology: an epidemiological survey in three in-patient psychiatric clinics. J. Psychiatr. Res. 47, 1095–1098. https://doi.org/10.1016/j.jpsychires.2013.04.001
Linkola, J., Fyhrquist, F., Ylikahri, R., 1979. Renin, aldosterone and cortisol during ethanol intoxication and hangover. Acta Physiol. Scand. 106, 75–82. https://doi.org/10.1111/j.1748-1716.1979.tb06372.x
Loosen, P.T., Chambliss, B., Pavlou, S.S., Orth, D.N., 1991. Adrenal function in abstinent alcoholic men. Prog. Neuropsychopharmacol. Biol. Psychiatry 15, 771–780.
Lovallo, W.R., Dickensheets, S.L., Myers, D.A., Thomas, T.L., Nixon, S.J., 2000. Blunted stress cortisol response in abstinent alcoholic and polysubstance-abusing men. Alcohol. Clin. Exp. Res. 24, 651–658.
Mander, A.J., Young, A., MacDonald, T.M., Williams, B.C., Waugh, C.J., Edwards, C.R., 1989. Blood pressure, renin-angiotensin-aldosterone axis and cortisol changes during withdrawal from alcohol. Alcohol Alcohol. Oxf. Oxfs. 24, 409–414.
Margraf, H.W., Moyer, C.A., Ashford, L.E., Lavalle, L.W., 1967. Adrenocortical function in alcoholics. J. Surg. Res. 7, 55–62. https://doi.org/10.1016/0022-4804(67)90035-2
McClung, C.A., 2007. Circadian rhythms, the mesolimbic dopaminergic circuit, and drug addiction. ScientificWorldJournal 7, 194–202. https://doi.org/10.1100/tsw.2007.213
McCulley, W.D., Ascheid, S., Crabbe, J.C., Rosenwasser, A.M., 2013. Selective breeding for ethanol-related traits alters circadian phenotype. Alcohol 47, 187–194. https://doi.org/10.1016/j.alcohol.2013.01.001
Mendelson, J.H., Ogata, M., Mello, N.K., 1971. Adrenal function and alcoholism. I. Serum cortisol. Psychosom. Med. 33, 145–157.
Merry, J., Marks, V., 1972. The effects of alcohol, barbiturate, and diazepam on hypothalamic-pituitary-adrenal function in chronic alcoholics. Lancet Lond. Engl. 2, 990–991.
Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 6, e1000097. https://doi.org/10.1371/journal.pmed.1000097
Mukai, M., Uchimura, N., Hirano, T., Ohshima, H., Ohshima, M., Nakamura, J., 1998a. Circadian

rhythms of hormone concentrations in alcohol withdrawal. Psychiatry Clin. Neurosci. 52, 238–240. https://doi.org/10.1111/j.1440-1819.1998.tb01051.x
Mukai, M., Uchimura, N., Hirano, T., Ohshima, H., Ohshima, M., Nakamura, J., 1998b. Circadian rhythms of hormone concentrations in alcohol withdrawal. Psychiatry Clin. Neurosci. 52, 238–240. https://doi.org/10.1111/j.1440-1819.1998.tb01051.x
Murialdo, G., Filippi, U., Costelli, P., Fonzi, S., Bo, P., Polleri, A., Savoldi, F., 1991a. Urine melatonin in alcoholic patients: a marker of alcohol abuse? J. Endocrinol. Invest. 14, 503–507. https://doi.org/10.1007/BF03346853
Murialdo, G., Filippi, U., Costelli, P., Fonzi, S., Bo, P., Polleri, A., Savoldi, F., 1991b. Urine melatonin in alcoholic patients: a marker of alcohol abuse? J. Endocrinol. Invest. 14, 503–507. https://doi.org/10.1007/BF03346853
Park-Lee, E., Lipari, R.N., Hedden, S.L., Kroutil, L.A., Porter, J.D., 2012. Receipt of Services for Substance Use and Mental Health Issues Among Adults: Results from the 2016 National Survey on Drug Use and Health, in: CBHSQ Data Review. Substance Abuse and Mental Health Services Administration (US), Rockville (MD).
Pickering, L., Thorstensen, E.W., Riedel, C., Jennum, P.J., 2018. [Sleep and circadian rhythms]. Ugeskr. Laeger 180.
Prinz, P.N., Roehrs, T.A., Vitaliano, P.P., Linnoila, M., Weitzman, E.D., 1980. Effect of alcohol on sleep and nighttime plasma growth hormone and cortisol concentrations. J. Clin. Endocrinol. Metab. 51, 759–764. https://doi.org/10.1210/jcem-51-4-759
Raghavendra, V., Kulkarni, S.K., 1999. Reversal of morphine tolerance and dependence by melatonin: possible role of central and peripheral benzodiazepine receptors. Brain Res. 834, 178–181.
Röjdmark, S., Wikner, J., Adner, N., Andersson, D.E., Wetterberg, L., 1993. Inhibition of melatonin secretion by ethanol in man. Metabolism. 42, 1047–1051.
Rosenwasser, A.M., Fecteau, M.E., Logan, R.W., Reed, J.D., Cotter, S.J.N., Seggio, J.A., 2005. Circadian activity rhythms in selectively bred ethanol-preferring and nonpreferring rats. Alcohol 36, 69–81. https://doi.org/10.1016/j.alcohol.2005.07.001
Roth, T., Workshop Participants, 2009. Does effective management of sleep disorders reduce substance dependence? Drugs 69 Suppl 2, 65–75. https://doi.org/10.2165/11531120-000000000-00000
Rupp, T.L., Acebo, C., Carskadon, M.A., 2007. Evening alcohol suppresses salivary melatonin in young adults. Chronobiol. Int. 24, 463–470. https://doi.org/10.1080/07420520701420675
Sarkola, T., Mäkisalo, H., Fukunaga, T., Eriksson, C.J., 1999. Acute effect of alcohol on estradiol, estrone, progesterone, prolactin, cortisol, and luteinizing hormone in premenopausal women. Alcohol. Clin. Exp. Res. 23, 976–982.
Schmitz, M.M., Sepandj, A., Pichler, P.M., Rudas, S., 1996. Disrupted melatonin-secretion during alcohol withdrawal. Prog. Neuropsychopharmacol. Biol. Psychiatry 20, 983–995.
Schuckit, M.A., Gold, E., Risch, C., 1987. Plasma cortisol levels following ethanol in sons of alcoholics and controls. Arch. Gen. Psychiatry 44, 942–945.
Seitz, H.K., 2017. Alcohol and cancer-individual risk factors. Addict. Abingdon Engl. 112, 232–233. https://doi.org/10.1111/add.13664
Serafini, G., Muzio, C., Piccinini, G., Flouri, E., Ferrigno, G., Pompili, M., Girardi, P., Amore, M., 2015. Life adversities and suicidal behavior in young individuals: a systematic review. Eur. Child Adolesc. Psychiatry 24, 1423–1446. https://doi.org/10.1007/s00787-015-0760-y
Smith, N., Hill, R., Marshall, J., Keaney, F., Wanigaratne, S., 2014. Sleep related beliefs and their association with alcohol relapse following residential alcohol detoxification treatment. Behav. Cogn. Psychother. 42, 593–604. https://doi.org/10.1017/S1352465813000465
Steindl, P.E., Ferenci, P., Marktl, W., 1997. Impaired hepatic catabolism of melatonin in cirrhosis. Ann. Intern. Med. 127, 494.
Steindl, P.E., Finn, B., Bendok, B., Rothke, S., Zee, P.C., Blei, A.T., 1995. Disruption of the diurnal rhythm of plasma melatonin in cirrhosis. Ann. Intern. Med. 123, 274–277.
Swanson, G.R., Gorenz, A., Shaikh, M., Desai, V., Forsyth, C., Fogg, L., Burgess, H.J., Keshavarzian, A.,

2015. Decreased melatonin secretion is associated with increased intestinal permeability and marker of endotoxemia in alcoholics. Am. J. Physiol. Gastrointest. Liver Physiol. 308, G1004-1011. https://doi.org/10.1152/ajpgi.00002.2015
Swanson, G.R., Gorenz, A., Shaikh, M., Desai, V., Kaminsky, T., Van Den Berg, J., Murphy, T., Raeisi, S., Fogg, L., Vitaterna, M.H., Forsyth, C., Turek, F., Burgess, H.J., Keshavarzian, A., 2016. Night workers with circadian misalignment are susceptible to alcohol-induced intestinal hyperpermeability with social drinking. Am. J. Physiol. Gastrointest. Liver Physiol. 311, G192-201. https://doi.org/10.1152/ajpgi.00087.2016
Tana, M.M., Alao, H., Morris, N., Bernstein, S., Hattenbach, J., Rehman, R.B., Brychta, R., Sarkar, S., Zhao, X., Walter, M., Buckley, A., Chen, K., Rotman, Y., 2018. Fatigued Patients with Chronic Liver Disease Have Subtle Aberrations of Sleep, Melatonin and Cortisol Circadian Rhythms. Fatigue Biomed. Health Behav. 6, 5–19. https://doi.org/10.1080/21641846.2018.1408539
Targum, S.D., Wheadon, D.E., Chastek, C.T., McCabe, W.J., Advani, M.T., 1982. Dysregulation of hypothalamic-pituitary-adrenal axis function in depressed alcoholic patients. J. Affect. Disord. 4, 347–353.
Thayer, J.F., Hall, M., Sollers, J.J., Fischer, J.E., 2006. Alcohol use, urinary cortisol, and heart rate variability in apparently healthy men: Evidence for impaired inhibitory control of the HPA axis in heavy drinkers. Int. J. Psychophysiol. Off. J. Int. Organ. Psychophysiol. 59, 244–250. https://doi.org/10.1016/j.ijpsycho.2005.10.013
Tran, S., Chatterjee, D., Gerlai, R., 2015. An integrative analysis of ethanol tolerance and withdrawal in zebrafish (Danio rerio). Behav. Brain Res. 276, 161–170. https://doi.org/10.1016/j.bbr.2014.02.034
Välimäki, M., Pelkonen, R., Härkönen, M., Ylikahri, R., 1984. Hormonal changes in noncirrhotic male alcoholics during ethanol withdrawal. Alcohol Alcohol. Oxf. Oxfs. 19, 235–242.
Välimäki, M.J., Härkönen, M., Eriksson, C.J., Ylikahri, R.H., 1984. Sex hormones and adrenocortical steroids in men acutely intoxicated with ethanol. Alcohol Fayettev. N 1, 89–93.
Vengeliene, V., Noori, H.R., Spanagel, R., 2015. Activation of Melatonin Receptors Reduces Relapse-Like Alcohol Consumption. Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol. 40, 2897–2906. https://doi.org/10.1038/npp.2015.143
von Bardeleben, U., Heuser, I., Holsboer, F., 1989. Human CRH stimulation response during acute withdrawal and after medium-term abstention from alcohol abuse. Psychoneuroendocrinology 14, 441–449.
Waltman, C., Blevins, L.S., Boyd, G., Wand, G.S., 1993. The effects of mild ethanol intoxication on the hypothalamic-pituitary-adrenal axis in nonalcoholic men. J. Clin. Endocrinol. Metab. 77, 518–522. https://doi.org/10.1210/jcem.77.2.8393888
Wand, G.S., Dobs, A.S., 1991. Alterations in the hypothalamic-pituitary-adrenal axis in actively drinking alcoholics. J. Clin. Endocrinol. Metab. 72, 1290–1295. https://doi.org/10.1210/jcem-72-6-1290
Willenbring, M.L., Morley, J.E., Niewoehner, C.B., Heilman, R.O., Carlson, C.H., Shafer, R.B., 1984. Adrenocortical hyperactivity in newly admitted alcoholics: prevalence, course and associated variables. Psychoneuroendocrinology 9, 415–422.
World Health Organization (Ed.), 2011. Global status report on alcohol and health. World Health Organization, Geneva, Switzerland.
Ylikahri, R.H., Huttunen, M.O., Härkönen, M., Leino, T., Helenius, T., Liewendahl, K., Karonen, S.L., 1978. Acute effects of alcohol on anterior pituitary secretion of the tropic hormones. J. Clin. Endocrinol. Metab. 46, 715–720. https://doi.org/10.1210/jcem-46-5-715


Identification
Screening
Eligibility
Included
PUBMED
(n =140)
Records not included:
n = 68
Not on the subject
No original data (reviews, meta-analysis, commentaries)
Case reports
Preclinical trials
Studies on patients with cirrhosis
Studies on dynamic function tests (Insulin Hypoglycemic Test, Dexamethasone Test)
Records screened
(n =72)
Full-text articles assessed for eligibility
(n = 72)
Full-text articles excluded, with reasons (n=7)
Not on the subject : n=4
N <5 : n= 2
Case report/ Short commentary : n= 1
Studies included :
Melatonin : n = 15
Body core temperature : n = 3
Cortisol : n = 47
Actigraphy : n = 1

ACUTE

Melatonin :

Low consumption
- Plasma levels: Nal
- Urinary levels: Nal
- DMLO : Nal / delayed
- Nocturnal rise: Nal / delayed

Moderate/ high consumption
- Plasma levels: Nal /↓
- Urinary levels: Nal
- DMLO: Nal
- Diurnal rhythms: Nal
- Nocturnal rise: Nal
- Circadian phase shifts to light: Nal

Cortisol :

Low consumption
- Plasma levels: Nal

Moderate/ high consumption
- Plasma levels: Nal / ↑
- Urinary levels: Nal / ↑
- Decline over the day: Nal /↑
- CAR: Nal/ ↓

Temperature :

Low consumption
- Amplitude : ↓
- CBT at night: ↑
- CBT at day: ↓

Moderate/ high consumption
- No studies

DEPENDENCE

Melatonin :
- Plasma levels: ↓
- N/D ratio <1
- DMLO: Nal
- Median peak: ↓

Cortisol :
- Plasma level : ↑
- Urinary level : Nal / ↑
- Amplitude : Nal
- Difference between
- Maximum :Nal
- Minimum : Nal

Temperature :
- No studies

WITHDRAWAL

Melatonin :
- Plasma levels: ↓
- N/D ratio >1
- Minimum amount: ↑ (DT)
- Maximum amount: ↓ (DT)
- Amplitude: ↓ (DT)

Cortisol :
- Plasma level: ↑
- Urinary level: Nal / ↑
- Acrophase: delayed
- Cycle length : shorter

Temperature :
- mean CBT : ↑
- Amplitude : ↓
- Acrophase : delayed
- Mesor: Nal

ABSTINENCE

Melatonin :
- Plasma levels: Nal
- N/D ratio >1
- Maximal amplitude: Nal / ↓
- DMLO : Nal / delayed
- Rate of rise : Nal / slower
- Onset of the nocturnal plateau : Nal / delayed
- Acrophase : Nal / delayed

Cortisol :
- Plasma level : Nal
- Nocturnal cortisol pulsability : Nal

Temperature :
- mean CBT: Nal
- Amplitude : ↓
- Accrophase : Nal
- Mesor : Nal

Transient + dose dependent modifications of plasma cortisol and melatonin levels

Acute

Persistence or normalisation of cortisol and melatonin secretion within a month

Abstinence

Alcohol use disorder

Persistence of biological rhythms alterations

Withdrawal

Severe biological rhythms alterations correlated with alcohol withdrawal symptoms and complications (delirium tremens)

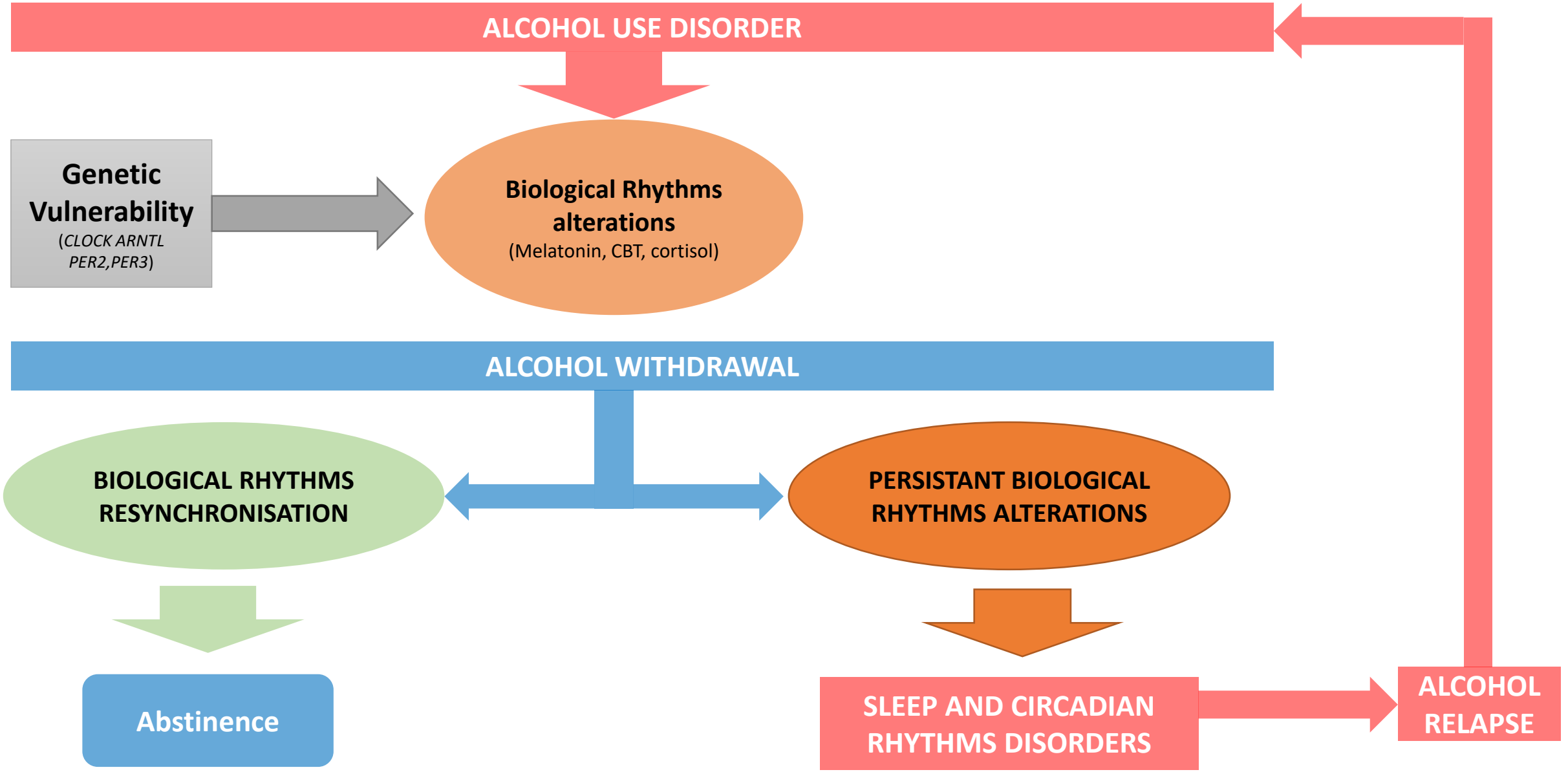

ALCOHOL USE DISORDER
Genetic Vulnerability
(CLOCK ARNTL PER2,PER3)
Biological Rhythms alterations
(Melatonin, CBT, cortisol)
ALCOHOL WITHDRAWAL
BIOLOGICAL RHYTHMS RESYNCHRONISATION
PERSISTANT BIOLOGICAL RHYTHMS ALTERATIONS
Abstinence
SLEEP AND CIRCADIAN RHYTHMS DISORDERS
ALCOHOL RELAPSE

Table 1: Studies examining Melatonin secretion and acute alcohol consumption, dependence, withdrawal and abstinence.

ACUTE (ACU), ALCOHOL USE DISORDER (AUD), WITHDRAWAL (WITH), ABSTINENCE (ABS)	Authors, year	Participants	Study design	Key findings		Comments
				Melatonin plasma levels	Urinary melatonin levels	
AUD + WITH	Danel et al, 2008	7 AUD with a reversed night/day ratio of 6SM/creatinine (<1) during alcoholization	Comparative study assessing night/day ratio of melatonin secretion of urine samples from 2000-0800 (night) and 0800-2000 (day) and comparing the urinary 6-SM levels in acute withdrawal phase (day 1, under benzodiazepines) and 15 days after beginning of withdrawal.		Normalization of 6SM/creatinine ratio 15 in 4 AUD 15 days after beginning of withdrawal.	Assessment of relative phase is limited by low temporal resolution of collection bins
AUD + ABS	Murialdo et al, 1991	10 AUD +10 HC	Comparative study assessing night/day ratio of melatonin secretion in urine samples collected from 2000-0800 (night) and 0800-2000 (day) and comparing the urinary 6-SM levels before and after 2 weeks of controlled abstinence.	Comparable melatonin level in the 2 groups after 2 weeks of controlled abstinence	1)Higher diurnal 24-hour urine melatonin levels in AUD before abstinence 2)Disruption of the physiological ratio between diurnal and nocturnal melatonin secretion in 6 out of 10 AUD (N/D ratio <1) before abstinence. Normalization of the physiological ratio after 2 weeks of controlled abstinence. 3) In contrast with chronic use condition in same patients, nighttime urinary melatonin levels were higher than daytime levels in patients, similar to that of HC.	Assessment of relative phase is limited by low temporal resolution of collection bins. Patients had significant depressive symptoms (mean value±SE: 25.7± 1.1).
AUD	Swanson et al, 2015	20 AUD + 17HC (11 day workers + 6 night workers)	Comparative study assessing hourly 24 hour dim light phase (between 13:00 and 12:00 h). Patients kept in dim light (<5 lux, measured every 2 hours)	1)Lower plasma melatonin AUC and decrease in median peak melatonin in AUD 2)Earlier mean DLMO in AUD than in HC night workers but similar to those in HC day workers 3)Significant correlation between plasma melatonin AUC and age in AUD group but not in HC group		
WITH + ABS	Mukaï et al, 1998	18 AUD, 2 of 18 had DT during withdrawal	Comparative study assessing serum melatonin levels (every 4 h) over consecutive 24 h during withdrawal, and at 1 month after withdrawal.	1)Normal circadian variation of melatonin during alcohol withdrawal in AUD with DT 2)Irregular serum melatonin concentrations rhythm during		

				withdrawal in patients with DT. Normal circadian rhythm was re-established 1 month after withdrawal.		
WITH	Schmitz et al 1996	10 AUD	Open study assessing plasma melatonin levels during withdrawal from alcohol (4 days and 4 nights). Bright light treatment (4500 lux between 07.00 and 09.00 and between 17.00 and 21.00), the rest of the day normal room-light was used) was applied during day 3 of the study.	Significant drop of melatonin secretion during the withdrawal and throughout the study		
ABS	Conroy et al, 2012	52 AUD + 19 HC	Comparative study assessing salivary melatonin collected at 30 min interval between 19h30 and 02h00 in HC and AUD abstinent from alcohol (3–12 wks since their last drink) in sleep laboratory recording rooms (dim incandescent light <40 lux).	1) Slower rate of rise and lower maximal amplitude of the melatonin rhythm in AUD group. Later DMLO in AUD group. 2)Larger phase angle difference between DLMO and the middle of the habitual sleep period reported in the diary in HC vs AUD		
ABS	Kuhlwein et al, 2003	11 AUD + 10 HC	Comparative study assessing plasmatic melatonin levels every 30 min from 10:00 PM to 6:30 AM in HC and AUD abstinent for more than 3 weeks.	1) Lower levels of melatonin during the early part of the night and delay in the onset of the nocturnal plateau or peak value of melatonin in AUD as compared with HC. 2)Correlation of nocturnal delay of melatonin with prolonged SOL.		
ABS	Fonzi et al, 1994	8 AUD + 8 HC	Comparative study assessing 24h plasma levels of melatonin in 8 HC and in 8 AUD males on the first day of ETOH withdrawal and after 14 days of controlled abstinence.	1)24 hour plasma melatonin mean levels were higher on acute withdrawal than after 14 days abstinence in AUD and than those found in controls. Loss of circadian periodicity in the acute withdrawal. Restoration of a significant 24h periodicity after 14 days of abstinence.		
ACU	Rupp et al, 2007	29 HC	Therapeutic study assessing salivary melatonin levels in HC after alcohol consumption (vodka: 0.54 g/kg for men and 0.49 g/kg for women) or placebo beverage over 30 min, ending 1 h before stabilized bedtime.	1)Reduction of melatonin level by 15% and 19% at 140 and 190 min after alcohol administration. 2) Unchanged DLMO phase.		
ACU	Swanson et al, 2016	22 HC (11 day workers + 11 night workers)	Therapeutic study assessing hourly plasma melatonin in HC before and after a 7-days period with daily alcohol intake (0.5 g of alcohol/kg)	1) Unchanged AUC plasma melatonin. 2) DLMO was unchanged in the day workers group and delayed in the night workers		

ACU	Harman et al, 2012	51 HC	Therapeutic study assessing 6-SMT in 24-h urine samples collected at baseline and at 4 wk (midpoint) and 8 wk (end) of each of the three diet periods (controlled diet plus a nonalcoholic placebo beverage or 15 or 30 g alcohol/day)		No significant changes in 6-SMT concentration by the alcohol treatment.	
ACU	Ekman et al, 1993	9 HC	Therapeutic study assessing plasma concentration of melatonin before and for 12h after the administration of 0, 0,5 and 1g ethanol/kg. Collected plasma samples at 1800, 2000, 2200, 2400, 0100, 0200, 0400, and 0700. Collected urine from 1900-2400 and 2400-0700 for urinary MT excretion. Lights on until 2300 when participants sent to bed; < 2 lux from 2300-0700.	1)Inhibition of the nocturnal melatonin secretion in a dose dependent manner during the first half of the night. (41% from the control at midnight for both ethanol doses, and 33% at 1h00 and 18% at 2h00 for patients with higher ethanol dose). Normalization of plasma melatonin level at 7h00 2) Plasma concentrations of melatonin had a diurnal rhythm in all groups (nocturnal rise starting after 22h00 and maximal occurring at 3h00-4h00). Nocturnal rise remain unchanged	No effect of ethanol on the urinary excretion of melatonin	High light levels until 23h00. Sleep/wake schedule prior to study were not controlled, light exposure history was unknown, and circadian phase was not assessed.
ACU	Danel et Toitou, 2006	11 HC	Therapeutic study assessing the circadian profiles of melatonin secretion in 11 HC exposed to 256 g of alcohol over 24 h (alcohol administered between 10: 00 on day 1 and 12:00 on day 2). Blood alcohol concentration were maintained between 0.29 and 0.78 g/l throughout the session. Blood samples collected from 1200 on day 1 until 1500 on day 2. Lux < 50	1) Consistent plasma melatonin concentrations between the two sessions. 2)Delay in the onset of melatonin secretion or in the time when the half-peak value was reached in 6 HC		Transient suppression in melatonin levels may have been missed by reported statistical analysis. Poor ecological validity of alcohol administration paradigm.
ACU	Rodjmark et al, 1993	7 HC	Experiment A-C: Alcohol administered at one of two doses (0.34 g/kg in A, 0.52 g/kg in B) at 1800, 2000, and 2200. Water was administered at same time points in Experiment C. Serum samples collected every 2 hours from 1800-0800. Collected urine from 2200-0700 for urinary melatonin excretion. For Experiments A-C: Lux 280-430 until 2300 when participants sent to bed. A 25W red light was used from 2300-0700	20% decrease in plasma melatonin levels for acute moderate ethanol dose (0,52g/kg)	Not modified under each of the 2 experimental conditions	High light levels <2300; unreported lux 2300-0700 (although red light likely to exert minimal suppression). Sleep/wake schedule prior to study was not controlled and light exposure history was unknown.Small sample sizes and between-group comparison

ACU	Burgess et al, 2016	**phase advance study** : 10 light drinkers **phase delay study :** 14 light drinkers	Therapeutic study assessing the effects of a single dose of alcohol on circadian phase advances and phase delays to light in HC. In the phase advance study, the laboratory sessions consisted of a baseline dim light phase assessment, sleep episode, alcohol (0.6 g/kg) or placebo, 2-h morning bright light pulse, and final phase assessment. In the phase-delay study, the laboratory sessions consisted of a baseline phase assessment, alcohol (0.8 g/kg) or placebo, 2-h late night bright light pulse, sleep episode, and final phase assessment.	1)No effects of a single dose of alcohol on circadian phase shifts to light.		

ACU : Studies on acute alcohol consumption ; ABS : Studies on patients abstinent from alcohol ; DEP : Studies on patients with alcohol use disorder ; WITH : Studies on patients during alcohol withdrawal ; AUD: patients with alcohol use disorder ; HC : healthy control ; AUC : area under curve ; DT : delirium tremens ; SOL : sleep latency

Table 2. Studies examining Body Core Temperature (CBT) and acute alcohol consumption, dependence, withdrawal and abstinence.

ACUTE (ACU), ALCOHOL USE DISORDER (AUD), WITHDRAWAL (WITH), ABSTINENCE (ABS)	Authors, year	Participants	Study design	Key findings Core body temperature (CBT)	Comments
ACU	Danel et al, 2001	9 HC	Therapeutic study comparing circadian temperature rhythm during a 26-h alcohol session to a 26-h placebo session. The two sessions were separated by 2 to 5 weeks. Rectal temperature was monitored every 20 min throughout the trial.	1) Standard hypothermic effect of alcohol in the early hours of the trial during the daytime. 2) Significant hyperthermic effect (10.36°C) during the night induced by alcohol consumption 3)Reduction in the amplitude of the circadian temperature rhythm (43%) due to the higher low point during the alcohol session, compared with the control session.	
ACU	Devaney et al, 2003	12 moderate drinkers (drinking on average, 2 days/week, S.D. = 1 and having an average of 4.3 standard drinks on these occasions)	Eight weeks study with a within-subjects design assessing the effect of alcohol consumption (BAC:0.10 g/100 ml in afternoon condition at 13h00 or in evening condition at 18h00) on CBT	1) **Acute effect of alcohol** : Decrease in CBT in afternoon condition (alcohol intake at 13h00) and elevating CBT in the evening condition. 2)**Delayed effect of alcohol** : dampening of the CBT between 23h30 and 08h30 after alcohol consumption irrespective of time of ingestion.	Potential masking effects such as ambient temperature, activity, food intake, were not completely controlled
WITH	Kodama et al, 1988	10 AUD (6 non depressive alcoholic + 4 depressive alcoholic)	Descriptive study longitudinally evaluating CBT during the day- and nighttime in six non-depressive and in four depressive alcoholics on the 3rd day and the 21th day of alcohol abstinence	1) Normal periods in all the patients throughout the study. 2) Phase advance of the circadian rhythms in all depressive AUD, and abnormal acrophase in 3 of the 6 non-depressive AUD on the 3rd and 4th days of alcohol abstinence. 3)Normal acrophase in 2 patients of the 4 depressives AUD and in 4 of the 6 non-depressives AUD on the 21st and 22nd days of alcohol abstinence. 4) Higher mean core temperature in the depressive than in the non-depressive AUD on the 3rd and 4th days but not on the 21st and 22nd days of alcohol abstinence	

AUD : Patients with alcohol use d*isorder; CBT : Core body temperature.*

Table 3. Studies examining Cortisol secretion and acute alcohol consumption, dependence, withdrawal and abstinence.

ACUTE (ACU), ALCOHOL USE DISORDER (AUD), WITHDRAWAL (WITH), ABSTINENCE (ABS)	Authors, year	Participants	Study design	Key findings		Comments
				Cortisol plasma levels	Urinary corticosterone levels	
AUD	Margraf et al, 1967	50 AUD + 50 HC		Elevated plasma cortisol level in AUD group (20 AUD vs 25 HC)	Excretion of tetrahydrocorticosterone rise (urinary metabolite of corticosterone) above normal in AUD group (5 AUD vs 3 HC)	
AUD	Mendelson et al, 1971		11-29 consecutive days of experimentally induced ethanol intoxication	1)Increase in serum cortisol levels in AD. 2)Correlation between elevated serum cortisol levels and a progressive increase in blood alcohol levels, indicating a general dose response relationship.		
AUD	Bertello et al, 1982	12 AUD with hypogonadal features + 20 HC	Descriptive study assessing levels of cortisol and testosterone by blood semples every 4 hours throughout a 24 hours span starting from 08h00 AM. Sleep in darkness from 22h00 to 06h00.	1)Circadian rhythms of plasma cortisol in AUD normally synchronized + surimperposable on that recorded in HC. 2)Similar rhythms in different AUD patients (amplitude, difference between maximum and minimum).		
AUD	Wand et al, 1991	14 AUD + 13 HC	Descriptive study assessing the impact of chronic alcohol abuse on the hypothalamic-pituitary-adrenal (HP A) with a 24-h UFC measurement, a dynamic testing of the HPA axis (CRH and ACTH stimulation tests) and a overnight metyrapone test for each subject. A submaximal Cortrosyn stimulation test was undergone in 8 subjects. Ovine CRH tests were performed at 1400 h. Blood was obtained for subsequent meas-urement of plasma ACTH and cortisol 20 min before and 0, 30, 60, and 90 min after the iv administration of CRH (1 microg/kg BW). The ACTH stimulation test was performed at 0800 h. Blood was obtained for measurement of serum cortisol 20 min before and 0 and 45 min after iv administration of 250 *ng* Cortrosyn [ACTH-(l-24)]. Mean alcohol consumption in AUD group was about 36+/-2 drinks.	Similar plasma cortisol levels in AUD and HC (0800 h, and 1400 h cortisol values).	2-fold higher twenty- four-hour urinary free cortisol levels in AUD than in HC.	

AUD	Hasselbalch et al, 1982	15 AUD (4 of them had cushingoid-like moon face and two of these also had buffalo hump).	Descriptive study assessing free urinary cortisol during 3 baseline days and for 3 days during administration of dexamethasone 0.5 mg 6-hourly.in AUD (daily alcohol intake of 100 g or more for at least 10 years).		1) Normal basal urinary cortisol excretion in all subjects. 2) No correlation between free urinary cortisol excretion and the Cushingoid stigmata.	
AUD+ ABS	Gianoulakis et al, 2003	152 non-drinkers (10-15g/ year) +154 light drinkers (Male : less than 30 g/day ; Female : less than 20 g/ day) + 151 high drinkers (Male : more than 30 g/day; Female : more than 20 g/day) + 151 abstinent AUD	Observationnal study assessing levels of plasma adrenal corticotropic hormone (ACTH), cortisol, and beta-END and pituitary beta-END in four subgroups: (a) nondrinkers, (b) light drinkers, (c) heavy drinkers, and (d) patients with alcohol use disorder in treatment. Blood sample were drawn at 9h30.	1)Higher plasma cortisol levels in the light drinking group and heavy drinking group compared with the nondrinkers group. 2)Higher plasma cortisol in the heavy drinkers group compared with the AUD. 3)Daily alcohol consumption could not predict the plasma levels of cortisol.		
AUD	Boschloo et al, 2011	-498 non-drinkers + 2112 moderate drinkers +337 heavy drinkers -No lifetime DSM-IV AUD (n = 2496), remitted AUD (>1 year; n = 243), and current AUD (≤1 year; n = 208).	Descriptive study assessing HPA-axis measures including the cortisol awakening response (area under the curve with respect to the ground [AUCg] and increase [AUCi]), evening cortisol and a 0.5 mg dexamethasone suppression test, all measured in saliva.	1)Higher basal cortisol levels (cortisol awakening response + evening cortisol) in heavy drinkers than moderate or non drinkers. 2)No association between lifetime diagnosis alcohol dependence and cortisol level (CAR / evening cortisol).		

AUD + ABS	Mander et al, 1989	19 paitients drinking more than 112 g ethanol per day for between 2 and 26 years (14 AUD were intoxicated on the day of admission = 176 g/day)	Descriptive study assessing blood pressure, renin-angiotensin-aldosterone axis and cortisol changes in patients with alcohol use disorder (mean ethanol consumption in the week prior to admission : 176 g/day) during acute intoxication (mean blood alcohol of 47 mmol/1)and 4 days of withdrawal from alcohol. Blood pressure, pulse and blood samples were taken between 5 and 5.30 p.m. after lying supine for 30 min.	1)Raised level of cortisol during acute intoxication (day 1) and a subsequent fall in plasma cortisol levels during abstinence. 2)No correlations between blood alcohol concentration and the subsequent changes over the first 24 h in cortisol.		
WITH	Targum et al, 1982	14 AUD with MDD + 14 AUD without MDD	Observational study assessing hypothalamic-pituitary-adrenal axis function. Baseline serum cortisols were collected at 8 a.m. and 4 p.m. on the day of administration of 1 mg of oral dexamethasone at 11:30 p.m. Post-dexamethasone cortisols were collected at 4 p.m. and 11:30 p.m. on the day subsequent to the administration of dexamethasone. Patients were all drug-free for a minimum of 7 days prior to the dexamethasone suppression test and were within 6-28 days of alcohol withdrawal at the time of the study.	Higher 8 AM cortisol in AUD with MDD group vs AUD without MDD group but similar values for basal 4 p.m. cortisols.		
DEP + WITH	Valimaki et al, 1984	32 AUD (7 males with testicular atrophy)	Descriptive study assessing serum concentrations of iodothyronines, cortisol, prolactin, testosterone and the respective tropic hormones, at the end of a long drinking period and subsequently during ethanol withdrawal over 1-2 weeks. Blood samples were drawn at 0800 hr after overnight fast of 12 h.	1) Slight increased of the morning serum cortisol level on admission in 2 patients and no diurnal rhythms of serum cortisol in 6 men . 2) Normalization of morning values and the diurnal rhythms and decreased by 18% of the mean serum cortisol morning level during the first week of abstinence. Serum cortisol evening levels decreased during the first week and significantly by 32% after two weeks of alcohol abstinence.	No changes were found in urinary free cortisol.	
WITH + ABS	Von bardeleben et al, 1988	20 AUD (8 with criterion for acute withdrawal, 12 met criteria for medium-term abstention) + 11 HC	Descriptive study assessing baseline corfisol secretory pattern and ACTH and cortisol reaponses to hCRH (100 microg) in 8 patients acutely withdrawn from ethanol and 12 patients who abstained from ethanol for 2 to 6 weeks. Baseline cortisol secretory were collected between 14h00 and 17h00 prior to hCRH stimulation. Following hCRH infusion at 1900h, the responses of ACTH and cortisol were calculated as net areas under time cotmmeera'yes (AUC) between 1900 and 2300 h. Acute withdrawal was defined as the time interval between 12 and 72 hours after cessation of ethanol intake. Medium-term abstention was defined as ranging from 13 to 42 days.	Elevated baseline cortisol during acute withdrawal from ethanol while medium-term abstention was associated with normalized cortisol secretion.		
WITH	Willendring et al, 1984	52 AUD (10% with withdrawal symptoms)	Descriptive study assessing 24-hr UFC (begun at 2300 hr) on the day of admission and basal serum cortisol, fasting blood sugar and serum glutamic - oxalic transaminase (SGOT) levels on the following morning of admission. A dexamethasone suppression test has been done on the day following admission (1mg per os dexamethasone was given at 23h00 and serum cortisol levels were obtained at 0800 and 1600 hr the following day) In any patient showing non-suppression (cortisol > 5.0 ~g/dl) at either time, the test was repeated one week later. In anyone showing persistent non-suppression at eight days, the DST was repeated again at 21 days. Any	High basal serum cortisol which significantly reduced after 3 weeks of abstinence.	High 24 hr UFC which were significantly reduced after three weeks of abstinence.	Only 10% objectively showed withdrawal or were treated for it on this admission.

			patient showing elevated basal serum cortisol (> 20 microg/dl) or UFC levels (> 150 microg/24 hr) on admission had those tests repeated at 21 days. The mean duration of abstinence at the day following the dexamethasone suppression test was 12, 5 days (median : 6 days).			
WITH	Adinoff et al, 1990	10 HC + 11 AUD	Descriptive study assessing plasma corticotropin (adrenocorticotropic hormone) and cortisol responses to ovine corticotropin releasing hormone (oCRH) and the cerebrospinal fluid levels of CRH and corticotropin in patients with alcohol use disorder at various durations of abstinence. 9 patients were evaluated at 1 week of abstinence, 9 patients were evaluated at 3 weeks of abstinence, 10 patients between 3weeks and 6 months of abstinence and 9 at more than 6 months of abstinence.	1)Basal total and free-cortisol levels at 1 and 3 weeks of abstinence similar to those of HC. 2) Similar baseline plasma total and free-cortisol levels and cortisol-binding globulin binding capacity were in AUD abstinent for 3 weeks to 6 months and for greater than 6 months with HC. 3) Significantly altered hypothalamic-pituitary-adrenal axis functioning up to 3 weeks following the cessation of drinking, with a more subtle impairment present for greater than 6 months following abstinence in AUD.		
WITH + ABS	Mukaï et al, 1998	18 AUD, 2 of 18 had DT during withdrawal	Descriptive study assessing circadian rhythms of hormones (cortisol, melatonin) in patients with alcohol use disorder during and 1 month after alcohol withdrawal. Serum hormone concentrations were measured six times (every 4 h) over consecutive 24 h during withdrawal, and at 1 month after withdrawal.	1)Abnormal cortisol rhythms during withdrawal (the maximum concentrations were reached between 20.00 and 00.00) which normalized after 1 month of withdrawal in patients with DT. Normal circadian rhythms during and after the withdrawal period In patients without DT. 2) Higher cortisol concentrations than 20 pg/nL in 2 patients with DT during withdrawal. Normal cortisol concentrations patterns in patients without DT.		
WITH	Merry et al, 1972	30 AUD + 30 HC	Descriptive study assessing : 1)Plasma cortisol levels from 9 A.M. to midday on day 1 of alcohol withdrawal. 2) Plasma cortisol levels from 9 A.M. to midday after 400-450 mg. amylobarbitone (depending on established dose effect) given orally at 9 A.M on day 2 of alcohol withdrawal. 3)Plasma cortisol levels from 9 A.M. to midday after 30-40 mg. diazepam (depending on established dose effect) given orally at 9 A.M on day 3 of alcohol withdrawal.	Higher plasma-9 A.M cortisol levels during withdrawal (12h) with normalization after ingestion of moderate amounts of alcohol, instead of rising as it did in HC.		

WITH	Costa et al, 1996	10 HC + 12 AUD	Descriptive study assessing during the first and second weeks after cessation of ethanol intake (abstinence for 3-9 days), the mean baseline ACTH and cortisol levels, measured in the morning (0800-08h30), the plasma corticotropin (adrenocorticotropic hormone, ACTH) and cortisol levels in response to both a stimulation test with human corticotrophin-releasing hormone (CRH = 100microg IV) and an insulin (0.15 UI/kg IV)-induced hypoglycaemia test (ITI). The cortisol response to a standard overnight dexamethasone (1mg) suppression test was also measured.	No differences between baseline cortisol value.		
WITH	Adinoff et al, 1991	6 AUD + 6 HC	Descriptive study assessing plasma cortisol concentration every 30 minutes for 24 hours in the early stage (first day after cessation) and the middle to late stage (the third day after cessation) of ethanol withdrawal syndrome as well as after the resolution of acute symptoms (8 days or more after cessation).	1)Higher plasma cortisol concentration in AUD group vs HC at day 1 of abstinence. No difference in plasma cortisol levels between HC and AUD after 8 day of alcohol abstinence. The highest plasma cortisol concentration on the 1rst day of withdrawal coincided with peak withdrawal symptoms 2) Shorter cycle length of plasma cortisol diurnal rhythmicity for 3 of 5 AUD on day 1 of withdrawal 3) Strong negative correlation between duration of the adjusted cycle length on day 1 and severity of withdrawal		
WITH + ABS	Fonzi et al, 1994 Melatonin and cortisol circadian secretion during ethanol withdrawal in chronic alcoholics.	8 AUD + 8 HC	Descriptive study assessing 24h plasma levels of melatonin and cortisol in 8 HC and 8 AUD on the first day of alcohol withdrawal and after 14 days of controlled abstinence.	1)Higher plasma cortisol level in acute withdrawal with normalization after 14 days of abstinence 2) Maintained24 hour periodicity on the first day of alcohol withdrawal and after 14 days of controlled abstinence. Delay in cortisol acrophase in acute withdrawal (day 1).		
WITH + ABS	Heinz et al, 1995	12 AUD + 14 HC	Descriptive study assessing serum concentrations of luteinizing hormone, follicle-stimulating hormone, testosterone, androstenedione, estradiol, sex hormone-binding globulin, cortisol, and prolactin were measured in 12 AUD once during withdrawal and once after 21 days of abstinence. Blood samples were drawn from all patients within the first 24 h following admission, between 08h00 and 10h00 in all cases. 6 of the patients were given clomethiazol for a period of between 2 and 4 days after the first blood sample had been taken. No other medication was permitted during the 21-day investigation period.	Higher plasma cortisol level in acute withdrawal with normalization after 21 days of abstinence.		

WITH + ABS	Iranmanesh et al, 1989	10 AUD + 7 HC	Descriptive study assessing pulsatile and circadian patterns of cortisol secretion during acute (3 to 16 days) or chronic (29-39 days) abstinence. Mean and integrated 24-hour serum concentration of cortisol were determined with blood samples every 20 minutes over a 24h period.	1) Higher mean and integrated serum concentration of cortisol during acute abstinence when compared with HC 2) Sustained abstinence in 7 AUD caused significant decreases in the mean maximal cortisol peak amplitude, mean 24-hour serum cortisol concentrations, interpulse valley mean and valley nadir concentrations. 3)Maintained circadian rhythmicity in AD, with a delay in the timing of the circadian acrophase during abstinence and with a amplitude of circadian cortisol rhythms exceeding normal in 5 of 10 patients with AUD. 4)Increased daily production of cortisol is a possible mechanism underlying the elevated serum cortisol concentration. 5)Analysis in on subject: increases in secretory burst amplitude, mass of cortisol released per burst and daily endogenous cortisol production rate during acute abstinence.		
ABS	Anthenelli et al 2001	67 AUD + 42 HC	Randomized, double-blind, placebo-controlled, crossover trial assessing plasma cortisol and ACTH levels were obtained at AM baseline and at half-hour intervals after D,L-fenfluramine (100 mg po). Two resting baseline blood samples were obtained after the men had been supine for 45 minutes and 70 minutes to measure their baseline hormone levels. Baseline blood pressure and pulse rate measurements were also taken twice, along with body temperature taken orally. At 9:00 AM, subjects orally ingested identical gelatin capsules containing either 100 mg of D,L-fenfluramine or placebo with 8 ounces of water. Blood samples (5 ml), body temperature, blood pressure, and pulse rate were obtained every 30 min for 5 hr after placebo or fenfluramine administration. The interval between the first and second laboratory sessions averaged 8.6 +/- 11.2 days (range, 2–88 days). Five minutes before ingesting the capsules and at regular half-hour intervals thereafter, the men completed a visual analog scale adapted from the Subjective High Assessment Scale. Mean duration of abstinence from alcohol was 119.3 +/- 387.2 days (range 26-998) at admission.	Lower baseline AM cortisol.		

ABS	Junghanns et al, 2003	31 AUD (19 relapsers + 12 abstainers) + 15 HC, 18 of 31 AUD had a current comorbid anxiety disorder	Descriptive study assessing the association of cortisol stress response during early abstention with relapse. The baseline values for serum cortisol, pulse, systolic and diastolic blood pressure were assessed at 13.00 (T1), after which the standardized Trier Social Stimulation Test was performed. The response parameters were investigated again immediately after the stress test (T2), and then after 20 (T3), 40 (T4) and 60 min . The patients were interviewed face to face about relapse at 6 weeks after discharge. The duration of abstinence before test was3.5 ± 0.5 weeks in relapsers and 4.6 ± 0.5weeks in Abstainers.	Similar baseline cortisol value in abstainers, relapsers and HC.		
ABS	Loosen et al, 1991	9 AUD + 9 HC	Descriptive study assessing nocturnal secretion of plasma ACTH and serum cortisol and their response to ovine corticotropin-releasing hormone (oCRH) were studied in acutely abstinent alcoholics (abstinence from alcohol for 15-39days, and no psychotropic medications) and normal men. Blood samples were drawn the first day at 22h every 15 min for 12 h. The following day oCRH (1mg) was administered at 1600h . Meal and activity schedule were standardized.	1) Similar nocturnal cortisol pulsability in AUD and HC (frequency, amplitude, or interpulse interval). 2) Similar mean nocturnal serum cortisol secretion were in AUD and HC (AUC).		
ABS	Inder et al, 1995	9 AUD + 9 HC	Descriptive study assessing cortisol, ACTH, CRH and AVP in a group of recently abstinent alcoholic. Subjects were studied after 10 days and within 6 weeks (mean 25+/- 3 days) of cessation of drinking. The levels of those hormones were measured every 20 minutes for 2 hours between 09h and 11h. 20 mg naloxone iv was administered at 11h (0 minutes) and further samples for the above hormones were taken at 15, 30, 45, 60, 90 and 120 minutes. On a separate occasion, again at 11h, oCRH 1microg/kg was administered, with samples for cortisol, ACTH and AVP taken at the same times.	Similar basal cortisol level between the 2 groups.		
ABS	Junghanns et al, 2007	24 AUD with short term abstinence + 12 AUD with long term abstinence	Descriptive study assessing the cortisol awakening response in saliva to compare 24 early abstainers (mean 21.977.6, range 10–36 days) with 12 alcohol-dependent patients with longer abstention periods (mean 116.8745.7, range 59–230 days) and looked for an association with sleep, especially rapid eye movement (REM) sleep of the preceding night. Lights were turned off between 2200 and 2330h depending on the patients' usual sleeping routine. Wake time was between 0600 and 0730 h in the morning to allow for 8h of sleep. Salivary cortisol was collected every 15 min beginning immediately upon awakening and ending 60min thereafter.	Stronger cortisol awakening response with higher cortisol levels 45 and 60 min after awakening in long term abstinence group.		

ABS	Bernardy et al 1995	14 HC + 40 AUD	Descriptive study examining urinary cortisol levels in in alcoholics abstinent from alcohol up to 4 weeks and controls at rest and following mental arithmetic and isometric handgrip stress. Testing began at 0800 h and consisted of: collection of a baseline urine sample (between 08H00 and 0830 h), completion of several questionnaires for alcohol consumption, a 20-min rest period, a 5-min isometric handgrip task, a 20-min rest period, a 10- min mental arithmetic task, and a 20-min recovery period. For each group, subjects were counterbalanced for task order. A 20-min interview assessed withdrawal symptoms and family history of alcoholism, and a poststress urine sample was collected at 11h15-11h30.	1)Similar baseline cortisol level in both groups 2) Attenuated cortisol response to the combined stressors in AUD group 3) Trend for an association between severity of withdrawal and poststress cortisol levels in AUD group. 4)Decreased adrenocortical response to biobehavioral stress in AUD abstinent up to four weeks, higher stress cortisol values in AUD with the most severe withdrawal symptoms.		
ABS	Lovallo et al 2000	10 HC + 19 AUD + 10 ADSD	Descriptive study assessing HPA function in the laboratory between 7:00 and 9:30 AM on control versus stress days in HC versus patients who were diagnosed as AUD or ADSD by DSM-IV criteria and who were abstinent for 3 to 4 weeks from alcohol and illicit drugs. Stress consisted of a 20-min public speaking challenge with preparation and delivery of two short speeches, ostensibly evaluated for quality of delivery, whereas control involved relaxing for the same period. Cortisol was measured in saliva collected at baseline, stress or control, and recovery period, and also at home at 9:00 PM on one of the two days.	1)Similar diurnal cortisol changes over the times tested in all groups. 2) ADSD values being higher than CT and AUD.		
ACU	Davis et al, 1983	20 HC	Descriptive study assessing effects of acute administration of ethanol on plasma cortisol. Sixteen HC were given oral ethanol (2.5 ml/kg vodka or gin) and four received intravenous infusions of ethanol (1 ml/kg), at two times of day, 0900 h and 1800 h. Blood sampling was performed at 30 min intervals for 2 h after the start of the infusion.	1)No specific rise in plasma cortisol during alcohol session (IV/ oral). 2)No circadian variation in response		
ACU	Linkola et al, 1979	7 HC	Cross-over study assessing the effect of ethanol intoxication and hangover on plasma renin activity, plasma aldosterone and plasma cortisol concentrations. During placebo session, they received deionized water 10 ml/kg at 8 am, and during alcohol session they received 10ml/kg of ethanol 15% (= 1.5g/kg). Blood samples were taken hourly in the evening from 6pm to 10pm, then at 12pm, 6, 8 and 10 am and at noon. Urine was collected 6-9 pm., 9-12 p.m.,0-6a.m.and 6-12a.m.	Initial suppression and a subsequent increase of plasma cortisol during ethanol session (biphasic effect).		
ACU	Aguirre et al, 1995	80 HC + 21 HC with acute alcoholic intoxication	Descriptive study assessing the possible relation between the endogenous opioid system and acute alcoholic intoxication in 21 subjects, of whom 13 (uncontrolled intoxication group) were drinkers who came to the emergency service with evident symptoms of drunkenness, and 8 were nondrinkers who consumed 1 g alcohol per kg body weight over a short period (controlled intoxication group). The control group consisted of 80 apparently healthy subjects (daily consumption ≤10-15 g of alcohol) and who have not consumed alcohol during the 48 h prior to testing. All participants were included in the study in accordance with the same criteria as in the controlled group. Blood samples were drawn between 7h00 and	No difference in plasma cortisol concentrations between the 2 groups.		

			10h00 In uncontrolled intoxication group, 15, 30, 45, 120 min before the during and 24h later in the controlled intoxication group and 0830 and 0930 h in the control group.			
ACU	Inder et al, 1995 (B)	12 HC (5 male, 7 female)	Cross-over study assessing plasma ethanol, cortisol, ACTH, cortlcotrophin- releasing hormone (CRH) and AVP following 1.1ml/kg of 95% ethanol or placebo. Blood samples were taken half- hourly for 4 hours. At least one week elapsed between each procedure.	Higher fall of cortisol along the diurnal rhythms on alcohol session than on placebo day.		
ACU	Prinz et al, 1980	5 HC	Cross-over study assessing cute and chronic effects of alcohol and alcohol withdrawal on sleep patterns and plasma GH and cortisol fluctuations occurring during sleep. The participants consumed a placebo drink for 3 baseline nights, alcohol (0.8 g/kg) for 9 nights, and a placebo drink on a final withdrawal night. All-night polygraphic sleep recordings and blood samples (every 20 min with a venous catheter) were collected for 1 placebo, 1 acute alcohol, 1 chronic alcohol (night 9), and 1 alcohol withdrawal night.	1)Similar daytime cortisol during alcohol and placebo sessions. 2) Unchanged temporal pattern during acute, chronic or withdrawal conditions. 3) Acute and chronic alcohol consumption reduced rapid eye movement sleep non significantly during the first half of the night, whereas slow wave sleep was increased significantly after acute alcohol, returning to baseline values on the chronic alcohol night. Similar rapid eye movement sleep and slow wave sleep from placebo sleep on the withdrawal night.		
ACU	Ekman et al, 1994	9 HC	Double blind cross-over study assessing serum ethanol and plasma ACTH, bêta-endorphin, and cortisol at 1 to 4 hr intervals for 12 hr after administration of 0.5 and 1.0 g ethanol/kg of body weight and placebo drinks between 19h00-19h45.	1)Higher plasma cortisol level at 400hr in acute high ethanol dose (1g/kg) than in acute moderate alcohol session (0.5g/kg) or during placebo session. Similar cortisol level during both alcohol session (0.5g/kg) and placebo session. 2) The nocturnal rise of plasma cortisol levels at 0400 hr, may be caused by the increased secretion of POMC (stress hormone secretion. Alcohol-induced nocturnal increase in the POMC-related peptides and plasma cortisol is a stress reaction. 3) Expected diurnal rhythm of plasma cortisol with the highest levels at 0700 hr in both alcohol sessions.		
ACU	Danel et al, 2006	11 HC	Single-blind, randomized, crossover study that compared a 26 h alcohol session and a 26 h placebo session. During alcohol session, 256 g of ethanol were administered between 10:00 h on day 1 and 12:00 h, and blood alcohol concentration were maintained between 0.5 g/l and 0.7 g/l throughout the session. Lights were off between 22:00 and 06:00h. Blood samples were collected to measure blood alcohol concentration at five time points (12:00, 18:00, 24:00, 06:00, and 12:00 h) and for cortisol at 29 time points (12:00, 15:00, 18:00 h and then every 30 min between 18:00 and 04:00, 05:00, 06:00, 07:00, 08:00, 11:00, 15:00 h).	1)Similar cortisol level during alcohol and placebo sessions. 2) Unaltered circadian profiles by alcohol.		
ACU	Ida et al, 1992	First experiment : 7 HC / second experiment : 9 HC	In the first experiment, 7 HC were given ethanol (1.3 g/kg) in the form of a 43% alcohol solution of whiskey and water over a 30-min period (from 19:00 h to 19:30 h); blood samples were collected 30 min and immediately	1)Decrease of cortisol level at 150 and 180 min after ingestion during first experiment.		

			before the beginning of alcohol ingestion and then at intervals of 30 min for 180 min. In the second experiment, 9 HC males were given the same dose of alcohol, but this was given on 7 consecutive evenings and the hormonal changes were examined on the 1st and 7th days, only at 30 and 60 min after alcohol ingestion began (during the period that blood ethanol levels were ascending to their peak).	2)Unchanged plasma cortisol level by acute or repeated alcohol ingestion during second experiment.		
ACU	Jenkins and Connolly, 1968	15 HC (8 females + 7 males) + 4 HC with lesions (2 with lesions of the hypothalamus and two with lesions of anterior pituitary)	Descriptive study assessing the effect of ethanol given intravenously in a dosage of 1 ml./kg on adrenocortical function. Blood samples were taken before and at the end of the ethanol infusion; thereafter samples were taken at intervals of 30 minutes for two and a half-hours.	Increase in plasma cortisol levels 90 minutes after acute ethanol administration at concentrations above 100 mg/100 ml (except for 2 patients with pituitary lesions).		
ACU	Gianoulakis et al, 1989	33 HC with high familial risk for future development of alocholism + 20 HC with low familial risk for future development of alcoholism	Cross-over study assessing pituitary beta-endorphin and cortisol response to ethanol in HC with high and low risk for future development of alcoholism. Blood sample was taken at 9:00 a.m., then the subject drank a placebo drink or an ethanol solution (0.5 g ethanol/kg.). Additional samples were taken at 15, 45 and 120 minutes post-drink.	Small increase after alcohol intake in plasma cortisol level in the high risk group but not in the law risk group (20% increase at 15 min and return to baseline by 120 min).		
ACU	Frias et al, 2002	21 HC with acute alcohol intoxication +27 HC	Descriptive study assessing blood samples from adults of both sexes who arrived at the emergency department with evident behavioural symptoms of drunkenness (AAI) or from adult volunteers with nil consumption of alcohol (controls). All blood sample were drawn at the same time of day, during the 3-h period from 12.00 to 03.00.	Increase in cortisol levels in both sexes in acute alcohol intoxication group.		Unknown amount of alcohol intake. Missing values of plasma cortisol level before alcohol consumption.
ACU	Ylikahri et al, 1978	12 HC	Descriptive study assessing plasma or serum concentrations of GH, TSH, LH, PRL, testosterone, cortisol, T4, and T3, and the values of the T3 uptake test in 12 healthy male volunteers for a period of 20 h after administration of one large dose of ethanol (1.5 g/kg BW).	1) Elevated concentration of cortisol in plasma during the whole 20-h period after ingestion of alcohol, as compared with the control values. 2)No correlations between individual concentrations of cortisol and the intensity of the hangover.		
ACU	Waltman et al, 1993	8 HC	Descriptive study assessing the effect of acute ethanol ingestion (0.75 g/kg) on the HPA axis in HC). Plasma ACTH/cortisol levels were determined basally and every 30 min over a 180-min period after the ingestion of placebo or ethanol.	No differences in plasma cortisol values after ethanol infusion.		
ACU	Valimaki et al, 1984 b	8 HC	Descriptive study monitoring the plasma or serum concentrations of testosterone, LH, FSH, PRL, cortisol, 17-hydroxyprogesterone, androstenedione, dehydroepiandrosterone, estrone and estradiol for a period of 48 hr after administration of one large dose of ethanol (1.75 g/kg BW) within the first 3 hr of the experiment. Blood samples were collected were collected 0, 2, 4, 12, 24, 36 and 48 hr after the start of drinking. Blood alcohol concentration reached a maximum of 1.51+/-0.08 g/l (mean +/- SEM) 4 hr after the start of drinking.	Serum concentration of cortisol increased by 152% ($p<0.01$) 4 hr after the start of drinking and remained above the control level until 24 hr.		
ACU	Bellet et al, 1970	9 HC	Cross-over study assessing plasma 1 l-OHCS level after administration of alcohol 1.5 ml./kg of body weight and placebo drinks at 9h30am. Blood samples were drawn on the day prior testing at 9h30 (control blood sample)	Increased plasma ll-hydroxycorticoid level in 8 of the 9 subject after alcohol intake (8-23 % increase).		

			and at 30, 60, 90, 120 and 180 minutes after testing for determination of ll-OHCS and ethanol levels.			
ACU	Thayer et al, 2006	542 HC (196 HC in the high use alcohol subgroup + 346 in the low use alcohol subgroup)	Descriptive study assessing the relationships among alcohol consumption, cortisol excretion, and heart rate variability. An overnight urine collection was collected from 9 pm on the night. Urine catecholamines were determined by HPLC and overnight urinary cortisol, standardized to gram excreted creatinine, used as our measure of HPA axis activity.		1)Higher urinary cortisol levels in men in the top tertile of self-reported alcohol consumption than in men in the lower two tertiles of alcohol consumption. 2)No correlations of urinary cortisol with alcohol use in both low and high alcohol use subgroup.	
ACU	Schuckit et al, 1987	30 HC sons of alcoholics + 30 HC sons of non-alcoholics.	Descriptive study assessing the pattern of change in plasma cortisol level following ethanol in response to alcohol in sons of alcoholics and controls. Three experiments were tested in random order : placebo, 0.75 mL/kg of ethanol, and 1.1 mL/kg of ethanol. Subsequent blood samples for cortisol determinations were obtained every 30 minutes over the next four hours.	Lower cortisol levels after drinking in the sons of alcoholics, at higher risk for the future development of alcoholism.		
ACU	Sarkola et al, 1999	61 HC for substudy A, 87 HC for substudy B and 10 HC for substudy C	Cross-over study evaluating the acute effect of alcohol on the hormone balance in women OC and OC-. All subjects participated randomly in one placebo- and one alcohol drinking event. The intervening time was 28 days, except for substudy C, which consisted of one placebo- and three alcohol- (0.34 g/kg, 0.68 g/kg, and 1.02g/kg diluted in 10% w/v) drinking events in random order, with intervals of 1 week or more in between. The drinking time was 30 min and started at 6 PM. Blood samples were taken at different time points (60 and 120 min for substudy A; 45 and 90 min for substudy B ; 40,90, and 150 min for substudy C).	No differences in cortisol levels during alcohol and placebo sessions were observed for OC- and OC+ subjects in the separate substudies or with substudies **A** and B combined.		
ACU	Badrick et al, 2008	3670 HC (381 heavy drinkers)	cross-sectional study evaluating relationship between indices of alcohol consumption and salivary cortisol concentration. Alcohol consumption was assessed in a self-completed questionnaire. Saliva samples were taken on waking, waking + 0.5, 2.5, 8, and 12 h, and bedtime for the assessment of cortisol.	1)Reduced slope of cortisol decline over the day in men heavy drinker. 2)Greater cortisol awakening in women heavy drinkers than in women moderate drinkers. 3) Positive association between cortisol and units of alcohol intake per week in men (3% increase in cortisol per unit of alcohol consumed).		Non-standardized self-completed questionnaire

ADSD: alcohol and stimulant dependent; AUD: patients with alcohol use disorder; DT: delirium tremens; HC: healthy control; MDD: Major Depressive Disorder; OC +: oral contraceptives users; OC-: oral contraceptives nonusers.