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Perspective

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# Sleep and circadian influences on blood alcohol concentration

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## Abstract

**Study Objectives:** Anecdotally, adults reach higher levels of subjective intoxication on days they are fatigued or sleep-deprived, but sleep is not typically discussed as a predictor of blood alcohol concentration (BAC) in clinical settings. To inform clinical work and future research, this perspective reviews data examining the impact of sleep (process S) and circadian (process C) factors on indicators of BAC in humans and animal models.

**Methods:** Literature searches of medical and psychological databases were conducted to identify articles that manipulated sleep/circadian factors and reported effects on indicators of alcohol pharmacology (e.g. BAC, alcohol metabolism).

**Results:** Of the 86 full-text articles reviewed, 21 met inclusion criteria. Studies included manipulations of time of day, circadian phase (evidence for process C), and time in bed (evidence for process S). Evidence for time-of-day effects on alcohol pharmacology was most compelling. Studies also provided evidence for circadian phase effects, but failed to find support for time-in-bed effects. Although results were not uniform across studies, most evidence from human and animal models indicates that peak BACs occur toward the beginning of the biological day, with some studies indicating slower alcohol elimination rates at this time.

**Conclusions:** Circadian factors likely influence alcohol pharmacokinetics, perhaps due to altered elimination of alcohol from the body. This means that individuals may reach higher BACs if they drink during the morning (when, for most people, circadian alerting is low) versus other times of the day. Alcohol prevention and intervention efforts should highlight sleep/circadian health as a potential contributor to alcohol-related harm.

**Key words:** sleep; circadian; alcohol; pharmacokinetics; intervention

### Statement of Significance

Both poor sleep health and heavy alcohol use are common among adults in the United States. This study reviewed animal and human research testing sleep and circadian influences on indicators of blood alcohol concentration. Results suggest the strongest evidence for time-of-day effects on alcohol pharmacokinetics, such that BACs tend to be higher in the morning than at other times of day.

## Introduction

Alcohol use disorder is among the most common disorders in the United States, with a lifetime prevalence rate of almost 30% [1]. Binge drinking, or the consumption of high doses of alcohol in a single sitting (typically operationalized as 4 + drinks for women and 5 + drinks for men), is also prevalent among adults in the United States. Specifically, past-month rates of binge drinking are ~25%–30% among young adults [2] and have been increasing among middle-aged and older adults (~15%) [3]. Given the economic cost of this style of drinking [4], efforts to prevent and intervene in heavy drinking are a public health priority. Improved sleep has received increasing attention as a strategy to reduce alcohol-related harm, due to high rates of comorbidity between sleep and alcohol use disorders and potentially intersecting neurobiological mechanisms [5, 6]. However, little is known about how or why sleep might impact alcohol use outcomes.

Both heavy-drinking young adults and those with alcohol use disorder report higher subjective levels of alcohol impairment

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on days they are fatigued or sleep-deprived [7, 8]. It is possible that disturbed sleep leads to stronger subjective intoxication by increasing levels of sedation [9]. However, it is also plausible that sleep or circadian factors have a direct impact on blood alcohol concentration (BAC) [10]. The effects of ingested alcohol on the body, including the nervous system (pharmacodynamics), depend on the concentration of alcohol in circulation. In turn, the concentration of alcohol in circulation depends on how ingested alcohol is absorbed into, distributed through, and eliminated from the body (pharmacokinetics). Sleep/circadian influences on either of these processes (pharmacodynamics or pharmacokinetics) may explain why individuals report higher levels of subjective intoxication when their sleep is disrupted.

The two-process model [11] has been widely adopted to explain the regulation of sleep. The model postulates two sleep regulatory processes: homeostatic sleep drive (process S) and the circadian pacemaker (process C). Homeostatic sleep drive describes one's natural "drive" or propensity for sleep, which increases during wakefulness and decreases during sleep. As such, one's sleep drive will be stronger the longer it has been since they slept. In addition, the circadian pacemaker (or "circadian clock") creates natural, roughly 24-hour oscillations in alertness/sleep propensity. According to the model, these processes are independent but interactive. When sleep drive rises (during wake) to the upper boundary of circadian alerting, it triggers sleep; and when it falls (during sleep) to the lower boundary of circadian alerting, it triggers wake [11]. This model is a useful heuristic for understanding sleep regulatory influences on other processes, including metabolism [12], mood [13], and (in this case) BAC.

To determine the tenability of the hypothesis that sleep/circadian factors impact alcohol pharmacology and to inform future research and clinical work in this area, we reviewed data examining the impact of sleep and circadian factors on indicators of BAC in both human and animal models. We hypothesized that sleep and circadian factors would impact BAC, but we did not have specific hypotheses about which aspect of sleep would be most impactful (e.g. process S vs. process C; sleep duration vs. sleep timing). Similarly, we did not have a priori hypotheses about which aspect of alcohol pharmacology might be impacted (e.g. kinetics vs. dynamics; absorption vs. elimination).

## Methods

This study is not intended as an exhaustive review of all possible scientific evidence. Rather, we aimed to systematically review an illustrative body of evidence supporting and/or challenging the hypothesis that sleep and circadian factors influence BAC. Searches of psychological, medical, and educational databases were conducted to identify studies that (1) manipulated sleep/circadian factors and (2) reported manipulation effects on indicators of alcohol pharmacology; e.g. BAC, breath alcohol concentration (BrAC), or alcohol metabolism.

### Search strategy

Searches were conducted on PsycINFO, Academic Search Premier, Web of Science, PubMed, and SCOPUS using Boolean search strategies. For example, the search terms for PsycINFO included *keywords* ([alcohol* OR ethanol] AND [sleep OR insomnia OR "circadian rhythm" OR "circadian clocks" OR "biological clocks" OR "biological rhythms" OR chronobiology]) and *any field* (metabolism OR biosynthesis OR pharmacokinetics OR pharmacology OR blood OR urine OR "breath alcohol concentration").

MBM screened and reviewed all articles for eligibility criteria, first reviewing titles and abstracts and then requesting full texts of those that were potentially relevant. Of the 1285 unique records identified, 86 full-text articles were reviewed. Of these, 16 met full eligibility criteria (manipulated sleep/circadian factors and reported effects on BAC, BrAC, or indicators of alcohol metabolism). An additional five studies were identified during the review process, resulting in a final sample of 21 studies. We were unable to access full English text for three studies (see Table 1). MBM and RUC reviewed and summarized all studies, consulting DMM and MAC to resolve discrepancies as needed.

### Outcome variables

Studies measured alcohol levels in the blood, urine, brain, breath, and liver. These measures are not the same and have different strengths/limitations; however, to summarize across studies, we will use the acronym "BAC" to refer to all of these measures (unless otherwise noted). Outcome variables included peak BAC ($C_{max}$), time to reach peak BAC ($T_{max}$), time for BAC to return to zero ($T_{min}$), absorption rate, and elimination rate. However, few studies reported all of these outcomes, and many included only breath alcohol measures.

## Results

Table 1 details the sample, manipulation, and relevant findings of the final 21 studies, four of which were conducted in non-human animal models and 17 of which were conducted in humans. Below and in Table 1, we organize studies by manipulation; specifically, studies manipulating time of day (e.g. chronokinetics), circadian factors, or sleep opportunity. Studies manipulating time of day and circadian factors provide evidence of "circadian" (process C) influences on BAC, while studies manipulating sleep opportunity (time in bed) provide evidence of potential "sleep drive" (process S) effects.

### Time of day

Fifteen studies manipulated the timing of alcohol administration within and/or across participants, and 13 found that BAC and/or elimination rates varied by time of day. We use the phrase "time of day" (rather than "circadian phase") to describe this manipulation because most studies administered alcohol at different times of day without confirming participants' circadian phase (e.g. *via* dim-light melatonin onset). This methodological inconsistency may account in part for inconsistent results regarding which time of day (morning, afternoon, or evening) was linked to the highest BACs following alcohol administration.

A plurality of studies found that participants reached higher BACs in the morning (~7–9 am) than in the afternoon or evening, given equivalent doses of alcohol [14–19]. Several studies' findings suggested faster absorption or slower elimination (either of which could explain higher BACs) in the morning versus evening [15, 17]. In contrast, two studies found no difference between BACs reached in the morning (8–9 am) versus afternoon or evening (4–5 pm) [9, 20]. Another study suggested higher BACs in the afternoon or evening than in the morning; specifically, alcohol was eliminated more quickly after drinking in the morning compared to drinking the evening before [21]. However, given evidence for elevated alcohol elimination rates the day after drinking [22], these effects could be attributed to drinking-induced changes in metabolic enzyme expression or function.

Although morning versus late afternoon/evening was the most frequent time of day comparison, one pair of studies compared

**Table 1.** Summary of Studies Testing Time of Day, Circadian, and Time in Bed Manipulations on Blood Alcohol Concentration

| Time of day | Sample | Manipulation | Findings |
|---|---|---|---|
| *Animal models* | | | |
| Soliman (1979) | Sixty-four adult male rats (8/time; strain = Sprague-Dawley) | Timing of administration: 1500, 1800, 2100, 0000, 0300, 0600, 0900, and 1200 | Alcohol administration (2 g/kg, i.p.) during the dark phase (2100–0900) of the light/dark cycle produced higher BACs than alcohol administration during the light phase (in blood, urine, brain, and liver). For blood, brain, and liver, maximum and minimum BAC were at 0300 and 1200, respectively. |
| Sturtevant (1988) | Forty-eight adult male rats (strain = Sprague-Dawley) | Timing of administration (0900, 1300, 1700, 2100, 0100, and 0500) and light/dark | BAC decreased at different rates after alcohol administration (1.5 g/kg, i.p.) at different times of day even in constant light or darkness. Elimination rate was always slowest at the time corresponding to transition from the light to dark phase of the light/dark cycle, and fastest toward the transition from the dark to light phase of the light/dark cycle. |
| *Human Studies* | | | |
| Jones (1974a) | Forty men in medical school (21–31 years; $n$ = 20 received alcohol) | Timing of administration: 1300–1700 versus 1700–2200 (between-participants) | Participants administered alcohol in the afternoon demonstrated a faster elimination rate (BrAC descended more quickly; target ~0.11 g/dL) than those administered alcohol in the evening. No difference in $C_{max}$, $T_{max}$, or absorption rate. |
| Jones (1974b) | Twenty participants in treatment for alcohol use disorder | Timing of administration: every 30 minutes from 1300 to 1700 and 1800 to 2100 on 2 consecutive days | BrAC (target ~0.15 g/dL) increased more rapidly in the afternoon than in the evening. Afternoon (but not evening) metabolism was faster on day 2 (prior drinking) than day 1 (prior abstinence). |
| LÖtterle (1989)* | Five healthy men | Timing of administration: 0715–0745 versus 1915–1945 | $C_{max}$ (target ~0.10 g/dL) was higher and $T_{max}$ was faster in the morning than in the evening. No difference in elimination rate. |
| Minors (1980) | Eight healthy young adults (20–25 years; five women) | Timing of administration: 1300, 1700, 2100, 0100, 0500, 0900, and 1300 | In both male and female participants, $C_{max}$ (target ~0.10 g/dL) was higher (highest at 0500), $T_{max}$ was faster, and disappearance was faster in the morning than afternoon/evening. Not significant when analyzed at the individual participant level. |
| O'Boyle (1995) | Sixteen healthy young men (19–25 years) | Timing of administration: 0800 versus 1600 | No difference in BAC curve (peak ~0.07 g/dL) in the morning versus evening. |
| Reinberg (1975)* | Six healthy young men (22–26 years) | Timing of administration: 0700, 1100, 1900, and 2300 | $C_{max}$ (target ~0.10 g/dL) was higher in the morning (peak 0700) than afternoon/evening. $T_{max}$ was faster in the morning than afternoon/evening. Absorption and elimination rates were faster in the morning than afternoon/evening. |
| Roehrs (1992) | Twelve healthy men (21–45 years) | Timing of administration: 0900 versus 1700 | No difference in BrAC (target 0.04 g/dL) in morning versus evening. |
| Rukmini (2021) | Twenty healthy young adults (21–30 years; three women) with normal (not early or late) circadian phase of entrainment | Timing of administration: every 4 hours during 40 hours of wakefulness | $C_{max}$ (target ~0.03 g/dL) was higher in the morning/afternoon than evening. $T_{min}$ longer in morning/afternoon than evening. Alcohol was eliminated faster with duration of drinking. No difference in $T_{max}$, absorption rate, or elimination rate. |
| Rutenfranz (1967)* | Six healthy men (23–38 years) | Timing of administration: 0930 versus 2130 | $C_{max}$ (target ~0.10 g/dL) was higher in the morning than at night. $T_{max}$ was not tested statistically, but appeared to be slightly faster in the morning than at night. No difference in elimination rate. |
| Sadler (2014) | 18 students (eight women) | Timing of administration: evening and next morning (hours not specified) | Faster elimination rate when alcohol was administered in the morning (after drinking) than the evening before in men and women. No difference in $T_{max}$ or distribution volume. Differences in $C_{max}$ were not tested statistically, but ranges provided suggest no difference (target ~0.080 g/dL for males, ~0.070 g/dL for females). |
| Sturtevant (1978) | Five healthy men (21–49 years) | Timing of administration: every 4 hours starting between ~0900–1130 | For four of the five participants, elimination rates were slowest between 1200 and 2000. Target BAC ~0.10 g/dL. |
| Wilson (1956) | Six human participants | Timing of administration: repeated for 36–48 hours | BAC (target ~0.05 g/dL) rose between 2000 and 1000 and fell between 1000 and 2000. Pattern not evident for shift worker. |
| Yap (1993) | Ten healthy men | Timing of administration: 0300, 0900, 1500, and 2100 | $C_{max}$ (target ~0.10 g/dL) highest at 0900. No difference in $T_{max}$, volume of distribution, elimination rate, or area under the blood ethanol curve. |

**Table 1.** Continued

| Circadian phase | Sample | Manipulation | Findings |
|---|---|---|---|
| *Animal models* | | | |
| Gamsby (2013) experiment 4 | Thirty-two adult mice (four male and four female per group; strain background = C57BL/6J) | *Per1* and *Per2* loss-of-function mutations | Alcohol administration (2 g/kg, i.p.) produced higher BAC in *mPer1* than *mPer2* mutant mice, and higher BAC in *mPer2* than double mutant or wild-type mice (see reference for sex differences). |
| Gauvin (1997) experiment 2 | Thirty adult male rats (10 per group; strain = Sprague-Dawley) | Cycling shift work schedule across 3 months and timing of administration (0800, 1600, and 2400) | Alcohol administration (2 g/kg, i.g.) 1 hr after an overnight shift (0800) produced higher BAC than 1 hour after a day shift (1600), and lower BAC 1 hour after an afternoon shift (2400) than 1 hour after a day shift. Alcohol absorption and elimination rate constant estimates did not differ after the overnight or day shift, but were both enhanced after the afternoon shift. |
| *Human studies* | | | |
| Van Reen (2011, 2013) | Twenty-six healthy young adults (21–25 years; nine women) | 20-hour forced desynchrony protocol: 0400, 1000, 1600, and 2200 | Descending BAC levels (target ~0.05 g/dL) were higher during biological day (no melatonin production) than biological night/early day (high melatonin production and melatonin offset). |
| **Time in bed** | **sample** | **manipulation** | **findings** |
| Lee (2015) | Sixteen healthy young men (18–27 years) | Time in bed: unrestricted versus 5 hours | No difference in $C_{max}$ (target ~0.05 g/dL) after sleep restriction. Alcohol was administered ~1230; 5 days between trials. |
| Roehrs (1989) | Twelve healthy young men (21–34 years) | Time in bed: 8 versus 10 hours | No difference in $C_{max}$ (target ~0.06 g/dL) as a function of time in bed. Alcohol administered ~0900; 7–8 days between trials. |
| Roehrs (1994) | Twelve healthy young men (21–35 years) | Time in bed: 4 versus 8 hours | No difference in $C_{max}$ (target ~0.05 g/dL) as a function of time in bed. Alcohol administered ~0900; 5 days between trials. |

*article not available in English. BAC, blood alcohol concentration. BrAC, breath alcohol concentration. $C_{max}$, peak BAC/BrAC. $T_{max}$, time to peak BAC/BrAC. $T_{min}$, time for BAC/BrAC to reach zero.

afternoon (1–5 pm) to evening (5–10 pm) alcohol consumption. Unfortunately, these results were also mixed, with medical students who drank in the evening demonstrating higher BACs than those who drank in the afternoon [23] and adults in treatment for alcohol use disorder demonstrating higher BACs in the afternoon than in the evening [22].

Perhaps providing some insight into these data, a study using continuous, low-dose oral alcohol administration found that BACs rose from 8 pm to 10 am (indicating an elimination rate slower than the loading or absorption rate) but then decreased from 10 am to 8 pm (indicating an elimination rate that exceeded the loading or absorption rate) [24]. This pattern was evident for all but one participant: a nurse working the night shift. This could indicate that alcohol metabolism depends specifically on circadian phase, not just time of day.

Three studies examined time-of-day effects on alcohol pharmacokinetics in mice or rats. These studies are discussed separately from human studies because the "night" (dark) phase of the light/dark cycle is the "active" period for these animals (whereas the opposite is true for humans). Testing the circadian rhythm of alcohol elimination rates in rats, Sturtevant and colleagues (1988) [25] found (1) that the elimination rate seems to demonstrate a truly "internal" rhythm, independent of exogenous light/dark cues, and (2) that the elimination rate is slowest at the onset of the dark phase, gradually increasing and reaching its peak near the transition from dark to light. Another study in rats also found that alcohol administration between 0000 and 0300 (at the beginning and middle of the dark phase) produced higher BACs than alcohol administration at other times of the light/dark cycle [26], which would be consistent with either faster absorption or slower elimination early in the "active" time of day. These rodent studies converge on the possibility of slower elimination rates earlier in the "active" period of the day, which is consistent with slower elimination in the morning compared to later in the day in humans. Together, these studies provide considerable evidence that peak BAC after alcohol dosing varies with the time of day of alcohol administration.

## Circadian factors

Van Reen et al. (2011, 2013) [27, 28] also varied the timing of alcohol administration, but within the context of a 20-hour forced desynchrony protocol. This design allows researchers to isolate circadian rhythms from homeostatic sleep drives. In this case, researchers considered four times of day corresponding to four different circadian phases (given controlled sleep/wake schedules; 4 am, 10 am, 4 pm, and 10 pm) and three homeostatic loads (relatively low, medium, and high; 4.25, 8.25, and 12.25 hours since sleep, respectively), with alcohol dosing targeting 0.05 g/dL. In their first analysis of these data [27], investigators found no difference in peak BAC by circadian phase. However, in a second analysis of these data [28], they found that circadian phase had a significant effect on BAC, but only on the descending limb of the BAC time-course. Specifically, descending BAC levels were higher during the biological day (circadian bin 4, no melatonin production) than during the biological night (bin 2, high melatonin production) or biological night/early day (bin 3, melatonin offset). This study builds on the previous studies by clarifying that circadian phase (not just time of day) may impact BAC.

Gauvin et al. (1997) [29] used a non-human animal model (male rats) to examine alcohol drinking and BAC as a function of circadian misalignments commonly seen in humans: short-term

photoperiod phase shifts ("jet lag") and long-term phase shifts like those experienced in rotating shift work. Rats drank more alcohol in the 3 days following a short-term phase advance (light earlier in the day). Rats also drank more alcohol the first morning following a short-term phase delay (light later in the day). When subjected to long-term phase shifts, rats drank the most alcohol at the beginning of the "lights out" period during the mimicked afternoon shifts (vs. day or midnight shifts). Critically, Gauvin et al. also report that peak BAC and elimination rate following an experimenter-administered alcohol dose (2 g/kg, intragastric) varied across work shifts. Specifically, peak BAC was lower—and alcohol absorption and elimination rate (kinetic) constants were higher—when dosing followed the mimicked afternoon shifts (vs. day or midnight shifts). In contrast, peak BAC was higher (but rate constants similar) when dosing followed the mimicked midnight shifts (vs. day or afternoon shifts). This highly controlled animal study suggests that circadian misalignment may impact not only drinking but also alcohol pharmacokinetics (e.g. absorption or elimination) and peak blood alcohol levels. However, the application to humans is unclear, since it was conducted in nocturnal rodents.

One additional study warrants mention here. Mice with loss-of-function mutations in the circadian clock genes *Period1* (*mPer1*) and *Period2* (*mPer2*) lack their species-typical circadian rhythms. In the absence of exogenous light cues, *mPer1* mice exhibit shortened sleep/wake cycles, *mPer2* mice show a shortened sleep/wake cycle that eventually becomes arhythmic, and *mPer1Per2* mice (double mutants) demonstrate no circadian oscillation [30]. In one study, Gamsby et al. (2013) [30] found that *mPer1*, *mPer2*, and *mPer1Per2* mice drink more alcohol than their wild-type counterparts. Critically, they also reached higher peak BACs following an experimenter-administered alcohol dose (2 g/kg, intraperitoneal). Specifically, *mPer1* mice reached the highest peak BACs, followed by *mPer2* mice, *mPer1Per2* mice, and wild-type mice; and this pattern was especially evident in female mice [30]. It is difficult to attribute these effects to circadian disturbances specifically, since Period-mutant rodents demonstrate circadian and non-circadian disturbances in physiology [31, 32]. However, this study does suggest an influence of circadian clock genes and their products on alcohol-related behavior and pharmacokinetics.

### Time in bed

In contrast to the literature reviewed above, three studies manipulated sleep by restricting time in bed, and none found differences in BAC. Specifically, Lee et al. (2015) [33] found no difference in peak BAC after "normal" (unrestricted) time in bed versus 5 hours in bed (BAC ~0.040–0.045 vs. ~0.041–0.048 g/dL, respectively). Similarly, Roehrs and colleagues found no difference in peak BAC when extending time in bed from 8 to 10 hours (peak BAC ~0.05 g/dL) [34] or when restricting time in bed from 8 to 4 hours (peak BAC ~.049 g/dL) [35]. Based on these studies, sleep restriction does not seem to impact BAC. However, all of these studies administered low doses of alcohol.

## Discussion

This review evaluated evidence testing the role of sleep and circadian factors on BAC. Although experimental studies in this area are scarce, findings from human and non-human animal models support the hypothesis that circadian factors influence the pharmacokinetics of alcohol, perhaps *via* its elimination from the body (i.e. metabolism and/or excretion). However, we still know little about which specific factors influence this process or how they do so.

### Recommendations for future research

#### *Assess circadian phase.*

Studies to date provide evidence for circadian (process C) influences on BAC. Although time-of-day effects were not uniform across studies, most evidence from human and animal studies indicates that peak BACs occur at the beginning of the biological day (or "active" phase, in rodent models), with some studies also indicating slower alcohol elimination rates at this time [14–18, 21, 24–26, 29]. These data seem consistent with a study in mice that found the highest rates of lethality from high-dose alcohol during the transition from light to dark [36], although lethality cannot be attributed conclusively to alcohol elimination or clearance rates (as opposed to control of heart rate or breathing). Furthermore, findings from at least two studies [24, 28] indicate that these effects may be due to circadian phase—and not just time of day. For example, this pattern of slower alcohol elimination and higher BAC in the morning was not evident for one participant who likely had an altered circadian rhythm (a nurse working the night shift) [24]. Thus, consistent with previous investigators [36], we speculate that time of day ("clock hour") is likely less influential than circadian phase. Given this, investigators are strongly encouraged to test (and manipulate) participants' phase of entrainment; for example, by testing rhythms of core body temperature or dim-light melatonin onset (see Rukmini et al. [17] and Van Reen et al. [28]). Although such testing can be cumbersome, researchers have developed take-home salivary test kits that are strongly correlated with lab-based measures ($r = 0.91$) [37].

Manipulate sleep drive. Evidence for "sleep drive" (process S) effects on BAC was more limited, as none of the studies reviewed found an effect of time in bed [33–35] or homeostatic load [27] on BAC. Importantly, none of these studies were designed to test sleep drive effects on alcohol pharmacokinetics; instead, change (or lack of change) in BAC was reported to aid in interpretation of manipulation effects on alcohol response (e.g. vigilance, sedation). Studies designed to test sleep drive effects on pharmacokinetics likely require greater variability in alcohol dosing. They may also need to disentangle sleep drive from circadian phase, as the plotting of breath alcohol concentrations depicted in Figure 2 of Van Reen et al. (2011) [27] seems to indicate that sleep drive and circadian phase interact in the prediction of BAC. Specifically, at relatively high homeostatic loads, alcohol administered at 2200 appears to result in quicker-decreasing BACs than alcohol administered at 1000; but this difference in BAC curve is not evident at medium or low homeostatic loads. This would be consistent with the predictions of the two-process model [11], but no studies have been designed to test this hypothesis.

Administer higher doses of alcohol. Human studies testing sleep drive effects on alcohol pharmacokinetics also involved target peak BACs ~0.04–0.05 g/dL [27, 33–35]. These low doses make sense from an ethical perspective, but represent a critical limitation to determining sleep/circadian influences on BAC for at least two reasons: (1) they are much lower than the doses many young adults consume on a night of heavy drinking (e.g. mean BrAC = .14 g/dL) [38] and (2) they are much lower than the doses used in the animal studies providing strongest evidence for sleep/circadian influences on BAC (2 g/kg; expected BAC ~0.08–0.12 g/dL) [26, 29, 30]. Low doses also may not provide sufficient range in BAC to observe potential sleep/circadian effects. Restricted range may help explain why previous studies have had difficulty detecting circadian modulation of BAC at the individual level—and why circadian modulation of BAC appears to be weaker than circadian modulation of other biological variables, such as core body

temperature, melatonin, or cortisol [17]. Human studies testing higher doses of alcohol are needed to draw strong conclusions regarding sleep/circadian effects (or lack of effects) on BAC.

Use intravenous alcohol administration. Evidence for circadian (if not sleep drive) effects on BAC raises the question of *how* sleep/circadian factors might be linked to BAC. The studies considered in this review pointed primarily to pharmacokinetic factors; most notably, slower elimination rates [14, 24, 25]. This could be due to downstream sleep/circadian effects on metabolic enzymes; for example, liver alcohol dehydrogenase or acetaldehyde dehydrogenase [39]. However, some well-designed studies did not find clear evidence of circadian influences on alcohol elimination [17]. This lack of consistency across studies may be due in part to variability in study design; for example, differences in alcohol dosing, food intake, and outcome assessment. When modeling alcohol elimination rates (which change slowly and vary considerably between individuals), intravenous administration of alcohol is recommended to eliminate the confounding effect of alcohol absorption in the gastrointestinal tract [17]. None of the reviewed studies administered alcohol intravenously, so it is difficult to state conclusively which aspect of alcohol pharmacokinetics might be affected (e.g. absorption vs. distribution vs. elimination).

Consider alcohol pharmacodynamics. Several studies indicate that sleep/circadian factors may also influence the effects of ingested alcohol on the body (i.e. pharmacodynamics). For example, the swimming activity of zebrafish increases when alcohol is administered in the morning but not in the evening [40]. In humans, some [9] (but not all [28]) studies found that alcohol produces subjective sedation during the day (when circadian alerting signals are low), but not in the evening (when alerting signals are high); and multiple studies have found that manipulation of sleep drive (*via* time in bed restriction [41] or extension [34]) alters alcohol's sedative properties. Thus, sleep/circadian factors seem to influence not only pharmacokinetics (e.g. alcohol metabolism) but also pharmacodynamics (e.g. sedation).

Account for bidirectional effects. It is also important to acknowledge the inverse of our hypothesized effect, as evening alcohol use has been found to suppress melatonin production [42] and alter sleep architecture [43–45] in adults. As such, experimental studies testing sleep effects on BAC also need to account for alcohol's effects on sleep. For example, if day 1 of a study involved alcohol administration following a normal night of sleep, and day 2 involved alcohol administration following a night of sleep deprivation, then day 2's sleep would be confounded by day 1's alcohol use. As such, future studies need to account for the potential bidirectional associations between sleep/circadian factors and alcohol use when relevant.

## Clinical implications

This review aimed to understand how the real-world experience of humans may be shaped by sleep and circadian influences on alcohol pharmacology (specifically, BAC). Adults across the spectrum of alcohol use, including those with alcohol use disorder, report higher levels of subjective intoxication on days that they are fatigued or sleep-deprived [7, 8]. Sleep deprivation tends to compound alcohol's sedative properties and cognitive performance-impairing effects [9, 41, 46], indicating that sleep may influence alcohol's effects indirectly. However, recent studies link sleep impairment to more alcohol-related problems (e.g. doing embarrassing things, taking foolish risks, losing memory of drinking events) when drinking quantities/frequencies remain stable [6, 47, 48]. The majority of studies in this review support the hypothesis that individuals may reach higher BACs as a function of sleep/circadian factors, with strongest evidence pointing to circadian effects on the body's ability to eliminate alcohol from circulation. This is an important finding because sleep is rarely discussed in alcohol prevention and intervention efforts—and if discussed, it is usually to address the effects of alcohol on sleep, not vice versa. However, heavy-drinking young adults are interested in associations between sleep and alcohol use [49] and tend to prefer personalized feedback on their BACs over the feedback typically included in brief alcohol interventions [50]. Thus, even if data are inconclusive, heavy drinkers should be armed with the knowledge that an all-nighter, misaligned sleep schedule, or perhaps just time of drinking could alter the way their body processes alcohol—and that this may change with consecutive days of drinking [21, 22].

## Conclusion

Sleep disturbance is ubiquitous in heavy-drinking populations, and the co-occurrence of sleep and alcohol disorders creates huge public health costs. This review found evidence for circadian (process C) influences on alcohol pharmacokinetics; most notably, peak BAC tends to be higher in the morning compared to other times of day (perhaps due to slower morning elimination of alcohol from the body). For adults entrained to daytime light, this means that "day drinking" may result in higher BACs not only because it allows for longer durations of drinking, but also because the body processes alcohol differently early in the day than in the evening. We found less evidence for sleep drive (process S) effects on BAC, though many studies have documented sleep drive effects on pharmacodynamic responses to alcohol (e.g. enhanced sedation, greater cognitive performance impairment) that may compound risk for alcohol-related harm. Given the between-study differences documented here, experimental studies designed specifically to test sleep and circadian effects on BAC are needed. We encourage studies assessing circadian phase, manipulating sleep drive, administering higher doses of alcohol, using intravenous alcohol administration, considering alcohol pharmacodynamics, and accounting for bidirectional sleep/alcohol effects. In the meantime, providers may consider warning individuals who drink alcohol that peak BACs may differ with time of day.

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## Author Contributions

MBM conceptualized the research question, which was refined in collaboration with RUC, DMM, and MAC, MBM and RUC reviewed all articles and wrote the first draft of the manuscript, with as-needed review and editing by all authors. All authors contributed to and have approved the final manuscript.

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