CIRCADIAN RHYTHM CHARACTERISTICS IN SUBSTANCE USE DISORDER PATIENTS WITH AND WITHOUT COMORBID MAJOR DEPRESSIVE DISORDER

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ABSTRACT

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INTRODUCTION

Circadian rhythms are, approximately, 24h. periodical biological rhythms (Czeisler et al., 1999) which coincides with light-dark cycle. These are endogenous rhythms generated by the biological clock or pacemaker which is located in the suprachiasmatic nucleus (Guo, Brewer, Lehman, & Bittman, 2006). Most of the biological (e. g. body temperature, hormonal secretion, sleep-awake) and behavioral parameters (e. g. alert, attention, memory) show circadian rhythmicity (Adan et al., 2012; Silva, Albuquerque, & Araujo, 2005; Wehr, 2001). Circadian rhythms are synchronized to external signals, also known as zeitgebers, being the main the light-dark cycle (Roenneberg et al., 2007) and changes in it requires phase readjustments.

Humans show differences in the circadian rhythms regulation, which can be assessed by self-reported questionnaires with adequate psychometric values (Di Milia, Adan, Natale, & Randler, 2013) and that consider several factors: preferable wake up time, level of activation once one have waked up, moment of the day when the individual feels better and timing at which the individual feels tired and the need to sleep (Adan & Almirall, 1991). By considering these factors, the questionnaires show scores in a dimension known as morningness-eveningness, which seems to follow a normal distribution (Natale & Cicogna, 2002). Moreover, it allows for classifying individuals in three circadian typologies: morning-, neither- and evening-type. The morning-type subjects tend to wake up and go to bed earlier and show a phase advance of their biological and behavioral circadian functions when compared to the evening-type. The neither-type population has been scarcely studied, but tends to maintain an intermediate position. The phase differences between extreme groups may vary from 2 to 12 h depending on the parameter considered (Adan et al., 2012) and are associated

with individual differences in the functioning of the endogenous circadian system (Levi & Schibler, 2007).

Several studies have shown that drug consumption has a negative effect on the circadian rhythmic expression which can last for weeks or months since the absence onset (Falcón & McClung, 2009). Subjects with substance abuse and/or dependence tend to show reduced amplitude of their circadian functions (v. g. body temperature and melatonin) as well as a time lag in the maximum values of those, being the higher during the absence syndrome (Adan, 2010, 2013; Conroy et al., 2012; Hasler, Smith, Cousins, & Bootzin, 2012; Hasler, Soehner, & Clark, 2014, 2015; Huang et al., 2010; Spanagel, Rosenwasser, Schumann, & Sarkar, 2005). In worst cases circadian rhythms may even disappear, which suggests a lesser quality of the wake and sleep periods (Adan, 2013). Circadian rhythmicity alterations results in a poorly adaptation to environmental changes and are associated to a wide range of biological and psychological issues (Barnard & Nolan, 2008; Huang et al., 2010). In this line, it has been proposed an interaction between substance use and circadian rhythmicity alterations which could trigger to a vicious circle by promoting the substance use disorder (SUD) as well as their pathophysiological consequences (Hasler et al., 2015).

Substance use is relatively common among people with any other comorbid mental disorder (v. g. psychotic, mood and anxiety disorder) which is known as dual diagnosis (Nesvåg et al., 2015; Toftdahl, Nordentoft, & Hjorthøj, 2016). Dual diagnosis patients tend to show higher use of medical services (Martín-Santos et al., 2006), rate of mortality (Hjorthøj et al., 2015), treatment failure (Carey, Carey, Maisto, Gordon, & Vanable, 2001), and cognitive impairment (Benaiges, Serra-Grabulosa, & Adan, 2013) as well as lower quality of life (Benaiges, Prat, & Adan, 2012) as compared to the SUD ones.

According to the World Health Organization, major depressive disorder (MDD) is considered as a major world problem affecting more than 350 million people around the world and it is also the worldwide first cause of disability. The relationship between circadian rhythms and depression has been studied along chronotype, physiological parameters and chronotherapy studies (Bechtel, 2015). Attending to chronotype, eveningness has been associated in most of the studies with the development of depressive symptomatology (even a MDD) and the use of antidepressant medication (Adan et al., 2012; Antúnez, Navarro, & Adan, 2014; Bahk, Han, & Lee, 2014; Chan et al., 2014; Merikanto et al., 2015; Toomey, Panizzon, Kremen, Franz, & Lyons, 2014), becoming considered as a risk factor for this disorder. Focusing on physiological data, alterations in the circadian rhythm of sleep-wake, body temperature and hormone secretion have been observed in MDD patients (Germain & Kupfer, 2008; Hartley & Quera-Salva, 2014; Malhi & Kuiper, 2013; Soria & Urretavizcaya, 2009). Specifically to temperature, inconsistent results have been observed along different studies (Ávila Moraes et al., 2013; Buysse, Monk, Kupfer, Frank, & Stapf, 1995; Schwartz et al., 1997; Souêtre et al., 1989; Szuba, Guze, & Baxter, 1997). Moreover, the evidence that bright light therapy, wake therapy and sleep deprivation therapy are useful for treating depression (Dallaspezia, Suzuki, & Benedetti, 2015; Golden et al., 2005; Oldham & Ciraulo, 2014) reinforces the link between circadian rhythms and MDD.

Co-occurrence of a SUD with a MDD (SUD-MDD), around the 11-27% in community studies (Kessler et al., 2003; Nesvåg et al., 2015) is associated with higher impairment and worse course of both disorders, worse functioning and higher risk of suicide as compared to patients without comorbidity (Blanco et al., 2012; Hasin et al., 2002; Worley et al., 2012).

SUD patients with and without comorbidity are commonly treated in therapeutic community or in ambulatory treatment. Therapeutic community treatment is based in a living-learning situation (Kennard, 2004) where everything that happens, mainly crisis, between the community members is employed as a learning opportunity (Magor-Blatch, Bhullar, Thomson, & Thorsteinsson, 2014). Ambulatory treatment, by the other hand, provides a situation where the patient lives in him habitual ambient and which is close to the treatment location. Both modalities are focused on psychosocial treatments which included group and individual treatment sessions and activities for improving the recovery (Kleber et al., 2006).

Taking in account the relevance of circadian rhythms and its association to SUD and MDD this study aims, for the first time, to examine the circadian characteristics (circadian typology, sleep-wake and distal skin temperature circadian rhythm) in male individuals with SUD diagnosis with and without MDD, in both therapeutic community and ambulatory treatment.

METHOD

Participants

Eighty male patients (40 ± 9.09 years) under treatment for SUD were enrolled in a cross-sectional design divided into two groups: one with SUD without comorbid psychopathology (n = 40; 20 from ambulatory and 20 from therapeutic community) and another with SUD with a comorbid major depressive disorder (SUD-MDD; n = 40; 20 ambulatory and 20 therapeutic community).

Materials and measures

Current diagnosis of SUD and MDD was confirmed using the Structural Clinical Interview for the DSM-IV Axis I Disorders (SCID-I; First, Spitzer, Gibbon, & Williams, 1999), which was previously provided by the psychologist of each center. Sociodemographic (age, marital status, social class, schooling and economic status) and clinical variables (psychiatric and substance use family history, age of onset of each disorder, relapses, abstinence periods, drugs used, suicidal attempts, presence of organic pathology and medication consumption) were collected with the SCID-I and a clinical interview designed for our study which also collected circadian info (wake up time, bedtime, presence of nap and total time spent sleeping).

Severity of SUD was assessed using the Drug Abuse Screening Test-20 (DAST-20; Skinner & Goldberg, 1986) through its Spanish version, which provides a total score from 0 to 20 (0 no addiction, 1-5 low, 6-10 intermediate, 11-15 substantial, and 16-20 severe addiction). Depressive symptomatology in MDD patients was assessed using the Hamilton Depression Rating Scale (HDRS; Hamilton, 1967) through its Spanish version, which provides a total scoring from 0 to 52 (0-7 absence, 8-13 low, 14-18 moderate, 19-22 substantial, and 22-52 severe depression).

Seasonal Pattern Assessment Questionnaire (SPAQ; (Rosenthal, Bradt, & Wehr, 1984) through its Spanish version (Adan, Natale, & Fabbri, 2006) was employed to identify seasonal disorder in the sample. This questionnaire assesses the presence and magnitude of seasonal variations along 7 items in a Likert-type response format (we avoided qualitative question) which provides a total scoring from 0 to 29. Cut-off points are stablished in 0-9 as no seasonal affective disorder (SAD), 10-11 and considering seasonal variations as a problem as sub SAD, and 12-29 and considering seasonal variations as a moderate problem as SAD.

Circadian typology was assessed with the Composite Scale of Morningness (CSM; Smith et al., 1989) through its Spanish version (Adan, Caci, & Prat, 2005). This scale contains 13 items in a Likert-type response format, being ten of them coded 1-4 and three 1-5, yielding a total score between 13 and 55. Spanish version cut-off points are stablished on 13-25 evening-type (ET), 26-36 neither-type (NT) and 37-55 morning-type (MT). Good reliability values have been observed in the employed version as well as in the original one with a Cronbach's α of .87 in both cases (Adan et al., 2005; Smith et al., 1989).

Distal skin temperature was assessed through a device known as Kronosensor (Sarabia, Rol, Mendiola, & Madrid, 2008) which collect physiological measures of distal skin temperature, body position, physical activity, light exposure and environmental temperature. Specifically, distal skin temperature was collected by a sensor known as *iButton® Thermochron DS1921H* (iButton, Maxim/Dallas Semiconductor Corp., USA) every two minutes during 48 hours. Parametric (cosinor method, Rayleigh vector, and Fourier analysis) and no parametric (interdaily stability, intradaily variability, maximum mean temperature in 5 consecutive hours and mean timing when it was reached, minimum mean temperature in 10 consecutive hours and mean timing when it was reached, and relative amplitude) analyses were performed for the collected data by the Circadianware™.

Procedure

Participants were included according to these inclusion criteria: 1) male gender; 2) aged 19-55; 3) According to DSM-IV-TR criteria (American Psychiatric Association, 2000) current diagnosis of a SUD, in remission and without relapses for at least three months and for the SUD-MDD group the additional criterion of MDD stabilized. Exclusion criteria were: 1) presence of any other psychopathology different from SUD

or MDD; 2) altered consciousness status, global cognitive deterioration, language comprehension problems or any other problem which could difficult the assessment. The assessment protocol was approved by the Research Committee of the University of Barcelona.

Data analysis

Group differences in demographic and clinical variables were explored with independent sample t-test for continuous data, and Chi-square test for categorical variables. An analysis of covariance (ANCOVA) considering the CSM as dependent variable and two multiple analysis of covariance (MANCOVA) considering the sleep-wake data and distal skin temperature parameters as dependent variable were performed with the diagnosis (SUD and SUD-MDD) and the type of treatment (ambulatory and therapeutic community) as independent variables. Age and time of abstinence were considered as a covariate to control for possible effects. Post hoc comparisons were adjusted by Bonferroni's correction. The partial eta square η_p^2 was obtained as a measure of the MANCOVA effect size and Cohen's *d* for the t-test. Statistical analyses were carried out using the SPSS/PC+ statistics package (version 17.0), and statistical tests were bilateral with the type I error set at .05.

RESULTS

Sociodemographic and clinical characteristics

Diagnostic groups showed no differences in years of schooling, number of substance use, time of abstinence, and SUD onset. SUD patients were more likely to be paired or married and to receive a disability pension, while SUD-MDD were more likely to be older, separated/divorced and to receive an elderly pension. Likewise, SUD-

MDD patients showed a greater percentage of medical disease comorbidity and higher amount of suicidal attempts.

Insert Table 1 Here.

Differences between treatment groups were the higher percentages of active and elderly pension patients in the ambulatory group, and those of unemployed, disability and no income patients in the therapeutic community group. Moreover, it was also observed a greater time of abstinence in ambulatory patients.

Regarding to the clinical tests employed, no differences were found by diagnostic nor by treatment groups for the DAST-20 nor for the SPAQ (see Table 1). Likewise, no differences by the type of treatment were found in HDRS scores of SUD-MDD patients (see Table 1).

Circadian typology and sleep-wake data

The circadian typology ANCOVA (see Table 2) did not revealed significant circadian typology differences for the diagnosis nor for the type of treatment. No interactive effect was observed. Moreover, no significant differences were observed in the patient distribution among the three circadian typologies by considering the diagnosis nor by considering the type of treatment.

T-test performed to compare our results with the normative data (Adan et al., 2005) revealed significant differences with higher scores (greater morningness) in all the groups: SUD [$t_{(170)} = 6.06$; $p < .001$; Cohen's d = 1.11], SUD-MDD [$t_{(170)} = 6.47$; $p < .001$; Cohen's d = 1.14]; ambulatory [$t_{(170)} = 6.28$; $p < .001$; Cohen's d = 1.12], and therapeutic community [$t_{(170)} = 6.24$; $p < .001$; Cohen's d = 1.12].

Insert Table 2 here.

Regarding the sleep-wake data (see Table 3) two significant differences were observed in the MANCOVA. The first difference observed was an earlier bedtime in the SUD-MDD patients as compared to the SUD (p = .005). The second difference was an earlier time to wake-up in therapeutic community patients as compared to ambulatory ones (p = .014).

Insert Table 3 here.

Distal skin temperature

Significant differences were found between diagnostic and type of treatment groups (see Table 4). Attending to diagnosis, SUD patients showed higher amplitude (p = .016), Rayleigh vector (p = .027), percentage rhythm (p = .009), relative amplitude (p = .046), relative amplitude multiplied by 10 (p = .038), and first harmonic power (p = .015). Regarding the type of treatment, ambulatory patients showed higher values in minimum temperature (p = .013) and mean temperature standard deviation (p = .020), as well as lower values in amplitude (p = .030), relative amplitude (p = .030), relative amplitude multiplied by 10 (p = .041) and accumulated power after twelve harmonics (p = .017).

The comparisons of the group means with the Spanish normative data (Batinga et al., 2015) revealed diverse significant differences. Attending to diagnosis, SUD patients values were greater in amplitude ($t_{(65)}$ = 3.10; p = .003; Cohen's d = 0.84), Rayleigh vector ($t_{(65)}$ = 11.77; p < .001; Cohen's d = 3.15), interdaily stability ($t_{(65)}$ = 16.71; p < .001; Cohen's d = 4.53), intradaily variability ($t_{(65)}$ = 42.16; p < .001; Cohen's d = 10.50), relative amplitude ($t_{(65)}$ = 2.40; p = .001; Cohen's d = 0.63), relative amplitude multiplied by 10 ($t_{(65)}$ = 3.37; p = .001; Cohen's d = 0.92) and minimum temperature after 10 consecutive hours ($t_{(65)}$ = 2.53; p = .014; Cohen's d = 0.69), while

SUD-MDD patients values were in Rayleigh vector ($t_{(65)}$ = 2.07; p = .042; Cohen's d = 0.57), interdaily stability ($t_{(65)}$ = 12.96; p < .001; Cohen's d = 3.49) and intradaily variability ($t_{(65)}$ = 56.84; p < .001; Cohen's d = 13.28). Regarding the type of treatment, ambulatory patients values were greater in Rayleigh vector ($t_{(65)}$ = 2.25; p = .028; Cohen's d = 0.61), interdaily stability ($t_{(65)}$ = 11.92; p < .001; Cohen's d = 3.22) and intradaily variability ($t_{(65)}$ = 56.84; p < .001; Cohen's d = 13.28), while therapeutic community patients were in amplitude ($t_{(65)}$ = 2.57; p = .012; Cohen's d = 0.70), Rayleigh vector ($t_{(65)}$ =7.03; p < .001; Cohen's d = 1.88), interdaily stability ($t_{(65)}$ = 20.73; p < .001; Cohen's d = 5.49), intradaily variability ($t_{(63)}$ = 40.15; p < .001; Cohen's d = 10), relative amplitude ($t_{(65)}$ = 2.40; p = .001; Cohen's d = 0.63), relative amplitude multiplied by 10 ($t_{(65)}$ = 4.10; p < .001; Cohen's d = 1.12) and minimum temperature after 10 consecutive hours ($t_{(65)}$ = 2.28; p = .026; Cohen's d = 0.62).

Insert Table 3 here.

Finally, Figures 1 and 2 show the functions and adjustment to cosinor of distal skin temperature by diagnosis and treatment groups, respectively. There can be observed that SUD and therapeutic community groups amplitude functions are greater than SUD-MDD and ambulatory ones, respectively.

Insert Figures 1 and 2 here.

DISCUSSION

This study examined, for the first time, the circadian characteristics (circadian typology, sleep-wake and distal skin temperature circadian rhythm) in SUD and SUD-MDD patients by considering its treatment modality (ambulatory and therapeutic community). We did not observe circadian typology differences but we did for sleep-wake and distal skin temperature between SUD and SUD-MDD patients as well as

between ambulatory and therapeutic community ones. Moreover, comparisons of our data with the norm allowed us to identify several differences which may carry important implications.

Attending to circadian typology, despite de absence of differences between the studied groups, we observed a greater tendency to morningness in the four groups as compared to the normative data. Although at first glance our results might contrast with those of previous studies that observed clear links between eveningness and SUD (Antúnez et al., 2014; Prat & Adan, 2011; Taylor, Clay, Bramoweth, Sethi, & Roane, 2011; Urbán, Magyaródi, & Rigó, 2011) and MDD (Antúnez et al., 2014; Fares et al., 2015; Hsu, Gau, Shang, Chiu, & Lee, 2012), it must be taken in account the fact that our sample was under SUD treatment as well as abstinent for, at least, three months. Considering these data all together with the fact that some studies have been proposed the morningness as a protective factor for the SUD and MDD (Adan, 2013; Adan et al., 2012; Antúnez et al., 2014), the greater tendency to morningness observed in our patients, as compared to the normal population, could be interpreted as the results of the recovery and good adherence to treatment, which is commonly oriented to establishing a morningness lifestyle.

Focusing on the sleep-wake data, we observed an earlier bedtime on SUD-MDD patients as compared to SUD ones which is in agreement with the higher (but no significant) tendency to morningness due to the relationship observed in previous studies with youth samples (Arrona-Palacios, García, & Valdez, 2015; Fabbian et al., 2016). On the other hand, therapeutic community patients showed an earlier wake up time as compared to the ambulatory group. This difference could be explained by the fact that therapeutic community patients have always to wake up at a determined time (it is controlled by the therapists), thing that is unable to be controlled in the ambulatory

treatment. Moreover, the sleep-wake data observed, which is inclined to the morningness, could be the result of the compliance of the therapeutic indications and, specifically in ambulatory patients, may constitute a sign of the recovery evolution.

Regarding the distal skin temperature circadian rhythm and its relationship with the diagnosis, greater amplitude, Rayleigh vector, percentage rhythm, relative amplitude and first harmonic power observed in SUD patients as compared to SUD-MDD revealed a greater circadian functioning in the firsts. As circadian alterations are frequent in SUD (Adan, 2010, 2013; Conroy et al., 2012) and MDD patients (Bunney & Potkin, 2008; Germain & Kupfer, 2008; Hartley & Quera-Salva, 2014), the co-occurrence of both disorders could result in a greater disturbance as it was observed in SUD-MDD patients due to their worse functioning. Attending to the type of treatment, therapeutic community group values were greater in amplitude, relative amplitude, lower minimum temperature, variability in their mean temperature, and greater twelve harmonic accumulated power, as compared to ambulatory ones. Observed differences, which suggest a greater circadian functioning in the therapeutic community group, could be the result of the therapeutic community treatment, which includes strict sleep, activity and food timing as well as the prohibition of stimulants (v. g. coffee, tea, cola and energetic drinks) consumption that may improve the circadian rhythmicity of these patients.

By comparing the four groups distal skin temperature values with those of the normal population, our results contrast with those obtained in studies with SUD (Adan, 2010, 2013; Danel, Libersa, & Touitou, 2001; Danel & Touitou, 2004) and MDD non-comorbidity patients (Ávila Moraes et al., 2013), as the circadian values found in our sample were adequate, even better, as compared to norms (Batinga et al., 2015). Specifically, amplitude and relative amplitude (both only in SUD and therapeutic

community), Rayleigh vector, interdaily stability, intradaily variability and minimum mean temperature after 10 consecutive hours (only in SUD and therapeutic community) were greater as compared to the normal population. The combination of these parameters may be considered as a good global circadian functioning index which implies a greater capacity to cope with environmental changes as well as a lower dependence on external signals (Adan, 2004; Barnard & Nolan, 2008).

Although it has been proposed that circadian rhythmic alterations produced by substance use persist during months and weeks since the start of the abstinence (Falcón & McClung, 2009), the good circadian rhythmic functioning observed in the four studied groups could be determined, similarly as it has been suggested for the circadian typology results, by the mean abstinence time of our sample, which is around eight months, as well as by the adherence to treatment of the sample. Specifically, the observed circadian hardiness (mostly in SUD and therapeutic community groups) could be the result of the recovery process, despite of a lengthy rhythmic alteration as a consequence of a chronic consumption, implying that the patient is adhered to the treatment and that he has broken the substance use-circadian alterations vicious circle (Hasler et al., 2015), which may reduce considerably the relapse risk. In this line, and according to the theoretical assumptions, circadian hardiness may be considered as a protective factor for the relapse and even as a biological marker of the SUD and SUD-MDD recovery status and relapse risk.

The current study has a number of limitations that should be considered when interpreting the results as well as addressed in future research. The first is the characteristics of the sample, relatively small and composed by male patients with an age range that does not represent the entire population. The second is the cross-sectional study design, which does not allow us to establish causal relationship between the

studies variables and factors. Third limitation lies in the variety of substance use in the sample, which could be a confounding factor unable to control. Fourth, the absence of a MDD non-comorbidity group limited us to show a complete vision of this issue, even though we compared our results with norms. Fifth, due to our sample characteristics conclusions made should be taken with caution and limited to those patients with three or more months of abstinence and that are under ambulatory or therapeutic community treatment.

To sum up, this is the first study examining the circadian characteristics (circadian typology, sleep-wake and distal skin temperature circadian rhythm) in SUD and SUD-MDD patients by considering its treatment modality. SUD and therapeutic community patients showed greater endogenous circadian power as compared to SUD-MDD and ambulatory, respectively. Likewise, the four studied groups have showed a greater circadian rhythmic functioning as compared to normal Spanish population. Our results allow us to suggest that the good circadian functioning observed may constitute a marker of the recovery status and relapse risk. Further studies, mainly longitudinal, should be developed to provide a more complete vision of the relationships between circadian rhythms in SUD and SUD-MDD patients regarding the onset, recovery and relapse.

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DECLARATION OF INTEREST

The authors report no conflicts of interest.

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Table 1. Sociodemographic and clinical data. Means and standard deviation or percentages, and statistical contrasts.

	SUD	SUD-MDD	Statistical contrast	Ambulatory	Therapeutic Community	Statistical contrast
Sociodemographic data						
Age (yr)	36.85 ± 10.36	43.03 ± 6.66	$t_{(78)} = 3.17$**	41.68 ± 9.24	38.20 ± 8.93	$t_{(78)} = 1.71$
Marital status			$\chi^2_{(4)} = 12.50$*			$\chi^2_{(4)} = 4.26$
Single	40%	50%		42.5%	47.5%	
Stable partner	17.5%	0%		10%	7.5%	
Married	22.5%	10%		22.5%	10%	
Separated/divorced	20%	37.5%		22.5%	35%	
Widower	0%	2.5%		2.5%	0%	
Years of schooling	11.03 ± 2.71	10.48 ± 2.98	$t_{(78)} = 0.86$	10.95 ± 2.83	10.55 ± 2.87	$t_{(78)} = 0.63$
Economic situation			$\chi^2_{(4)} = 11.12$*			$\chi^2_{(4)} = 10,46$*
Active	15%	10%		20%	5%	
Unemployed	35%	40%		32.5%	42.5%	
Disability pension	22.5%	7.5%		10%	20%	
Elderly pension	7.5%	32.5%		27.5%	12.5%	
No income	20%	10%		10%	20%	
Clinical data						
Medical disease comorbidity	20%	47.5%	$\chi^2_{(1)} = 6.77$*	40%	27.5%	$\chi^2_{(1)} = 1.40$
Hypercholesterolemia	0%	10%	$\chi^2_{(1)} = 4.21$*	5%	5%	$\chi^2_{(1)} = 0.01$
Respiratory system disease	10%	10%	$\chi^2_{(1)} = 0.01$	12.5%	7.5%	$\chi^2_{(1)} = 0.56$
Hepatitis	5%	12.5%	$\chi^2_{(1)} = 1.41$	12.5%	5%	$\chi^2_{(1)} = 1.41$
Diabetes	0%	10%	$\chi^2_{(1)} = 4.21$*	7.5%	2.5%	$\chi^2_{(1)} = 1.05$
AID	2.5%	5%	$\chi^2_{(1)} = 0.35$	5%	2.5%	$\chi^2_{(1)} = 0.35$
Other	10%	25%	$\chi^2_{(1)} = 3.12$	15%	20%	$\chi^2_{(1)} = 0.35$
Daily number of medication	0.63 ± 1.03	2.65 ± 1.92	$t_{(78)} = 5.89$***	2.03 ± 2.01	1.25 ± 1.46	$t_{(78)} = 1.92$
Substance use[a]	2.10 ± 0.93	2.58 ± 1.38	$t_{(78)} = 1.81$	2.40 ± 1.11	2.28 ± 1.28	$t_{(78)} = 0.47$
Alcohol	75%	87.5%	$\chi^2_{(1)} = 2.05$	75%	87.5%	$\chi^2_{(1)} = 2.05$
Cocaine	75%	75%	$\chi^2_{(1)} = 0.01$	72.5%	77.5%	$\chi^2_{(1)} = 0.27$
Cannabis	45%	35%	$\chi^2_{(1)} = 0.83$	42.5%	37.5%	$\chi^2_{(1)} = 0.21$
Hallucinogen	7.5%	15%	$\chi^2_{(1)} = 1.13$	12.5%	10%	$\chi^2_{(1)} = 0.13$

Opioid	5%	27.5%	$\chi^2_{(1)} = 7.44^{**}$	15%	17.5%	$\chi^2_{(1)} = 0.09$
Sedative	2.5%	17.5%	$\chi^2_{(1)} = 5.00^{*}$	10%	10%	$\chi^2_{(1)} = 0.01$
DAST-20	14.08 ± 2.98	14.74 ± 2.94	$t_{(78)} = 0.90$	13.87 ± 3.23	14.75 ± 2.69	$t_{(78)} = 1.22$
Number of suicidal attempts	0.18 ± 0.56	0.63 ± 1.17	$t_{(78)} = 2.15^{*}$	0.23 ± 0.48	0.58 ± 1.22	$t_{(78)} = 1.64$
Mean abstinence period (months)	8.45 ± 5.42	6.90 ± 4.47	$t_{(78)} = 1.40$	9.68 ± 5.37	5.68 ± 3.68	$t_{(78)} = 3.89^{***}$
Substance use disorder onset (year)	19.33 ± 6.52	17.78 ± 6.59	$t_{(78)} = 1.06$	18.95 ± 7.26	18.15 ± 5.84	$t_{(78)} = 0.54$
Major depressive disorder onset (year)		31.43 ± 9.15		31.25 ± 9.23	31.60 ± 9.30	$t_{(38)} = 0.12$
HDRS		7.85 ± 6.86		7.15 ± 7.79	8.55 ± 5.92	$t_{(38)} = 0.64$
SPAQ	7.30 ± 5.45	7.53 ± 5.85	$t_{(78)} = 0.18$	7.63 ± 5.72	7.20 ± 5.29	$t_{(78)} = 0.34$

SUD: Substance use disorder.

SUD-MDD: Substance use disorder with comorbid depression.

[a] Percentages will not equal 100 as each participant may take more than one substance.

*p < .05; **p < .01; ***p < .001

Table 2. Descriptive statistics (frequency, mean and standard deviation), normative data, chi-square statistic (χ^2), F tests and partial eta square (η_p^2) for the Composite Scale of Morningness (CSM) by diagnosis and type of treatment.

	Normative data	SUD	SUD-MDD	χ^2	F	η_p^2	Ambulatory	Therapeutic community	χ^2	F	η_p^2
CSM	30.23 ± 6.74	37.53 ± 6.47	38.28 ± 7.38		0.01	.001	37.95 ± 7.05	37.85 ± 6.86		0.06	.001
Circadian typology				0.23					0.01		
Morning-type	14.39%	60.0%	65.0%				62.5%	62.5%			
Neither-type	59.09%	35.0%	30.0%				32.5%	32.5%			
Evening-type	26.51%	5.0%	5.0%				5.0%	5.0%			

Table 3. Descriptive statistics (frequency, mean and standard deviation), chi-square statistic (χ^2), F tests and partial eta square (η_p^2) for the sleep-wake data by diagnosis and type of treatment.

	SUD	SUD-MDD	χ^2	F	η_p^2	Ambulatory	Therapeutic community	χ^2	F	η_p^2
Wake up time	7:37 ± 0:46	7:21 ± 1:05		1.20	.016	7:46 ± 1:06	7:12 ± 0:39		6.33*	.080
Bedtime	23:37 ± 0:45	23:06 ± 0:59		8.22**	.101	23:26 ± 1:08	23:17 ± 0:36		1.04	.014
Total time spent sleeping	7,95 ± 1.01	8.25 ± 1.04		2.69	.036	8.31 ± 1.00	7.90 ± 1.03		.87	.012
Presence of nap	30.0%	22.5%	0.58			32.5%	20.0%	1.61		

*$p < .05$; **$p < .01$

Table 4. Descriptive statistics (mean and standard deviation), normative data, F tests and partial eta square (η_p^2) of circadian rhythmic variables by diagnosis and type of treatment.

	Normative data	SUD	SUD-MDD	F	η_p^2	Ambulatory	Therapeutic community	F	η_p^2
Maximum temperature		36.15 ± 0.72	36.18 ± 0.57	0.44	.006	36.20 ± 0.69	36.13 ± 0.61	0.13	.002
Minimum temperature		30.47 ± 1.45	30.94 ± 1.67	0.97	.013	30.96 ± 1.64	30.45 ± 1.48	6.49*	.081
Mean temperature		33.40 ± 1.18	33.79 ± 0.94	1.73	.023	33.72 ± 1.13	33.47 ± 1.02	2.37	.031
Temperature standard deviation		1.59 ± 0.55	1.38 ± 0.54	2.10	.028	1.39 ± 0.49	1.58 ± 0.60	5.65*	.071
Mesor	33.69 ± 0.09	33.39 ± 1.19	33.78 ± 0.93	1.53	.020	33.69 ± 1.14	33.48 ± 1.02	1.88	.025
Mesor standard deviation		0.09 ± 0.03	0.08 ± 0.03	0.01	.001	0.08 ± 0.02	0.09 ± 0.03	1.66	.022
Amplitude	0.94 ± 0.11	1.38 ± 0.73	1.01 ± 0.61	6.08*	.076	1.07 ± 0.60	1.32 ± 0.76	4.93*	.062
Amplitude standard deviation		0.12 ± 0.04	0.11 ± 0.04	0.47	.006	0.11 ± 0.03	0.12 ± 0.04	2.24	.029
Acrophase	03:12 ± 00:18	01:50 ± 3:54	00:12 ± 2:42	3.26	.042	01:34 ± 4:07	00:28 ± 3:38	1.97	.026
Rayleigh vector	0.77 ± 0.03	0.96 ± 0.08	0.87 ± 0.25	5.08*	.064	0.87 ± 0.23	0.96 ± 0.14	3.40	.044
Rythm		32.27 ± 16.38	23.30 ± 13.61	7.19**	.089	26.14 ± 14.85	29.44 ± 16.39	1.83	.024
Interdaily Stability	0.30 ± 0.03	0.79 ± 0.15	0.75 ± 0.18	1.31	.017	0.76 ± 0.20	0.78 ± 0.12	0.17	.002
Intradaily Variability	0.23 ± 0.02	0.02 ± 0.02	0.02 ± 0.01	0.06	.001	0.02 ± 0.01	0.03 ± 0.02	0.11	.001
Relative Amplitude	0.03 ± 0.01	0.04 ± 0.02	0.03 ± 0.02	4.14*	.053	0.03 ± 0.02	0.04 ± 0.02	4.91*	.062
RA10	0.27 ± 0.003	0.40 ± 0.20	0.31 ± 0.17	4.47*	.057	0.32 ± 0.14	0.46 ± 0.24	4.35*	.055
M5	34.79 ± 0.11	34.90 ± 1.10	35.09 ± 0.74	0.30	.004	35.00 ± 0.86	34.95 ± 1.00	0.29	.001
TM5	04:07 ± 00:19	02:24 ± 3:38	01:37 ± 4:16	1.46	.019	01:58 ± 4:31	02:03 ± 3:22	0.01	.001
L10	33.07 ± 0.16	32.33 ± 1.51	32.95 ± 1.27	3.01	.039	32.82 ± 1.46	32.46 ± 1.38	2.92	.038
TL10	14:44 ± 00:54	16:44 ± 6:14	15:42 ± 5:22	0.14	.001	16:04 ± 5:40	16:22 ± 5:59	0.14	.002
1st harmonic power		1.22 ± 1.32	0.68 ± 0.74	6.21*	.077	0.78 ± 0.78	1.12 ± 1.33	3.70	.048
12th harmonic accumulated Power		2.12 ± 1.71	1.46 ± 1.18	3.79	.049	1.46 ± 1.11	2.13 ± 1.75	6.00*	.075

RA10: Relative amplitude multiplied by ten; M5: Maximum temperature in 5 consecutive hours; TM5: Time when the maximum temperature in 5 consecutive hours was reached; L10: Minimum temperature in 10 consecutive hours; TL10: Time when the minimum temperature in 10 consecutive hours was reached.

*$p < 0.05$

a.

b.

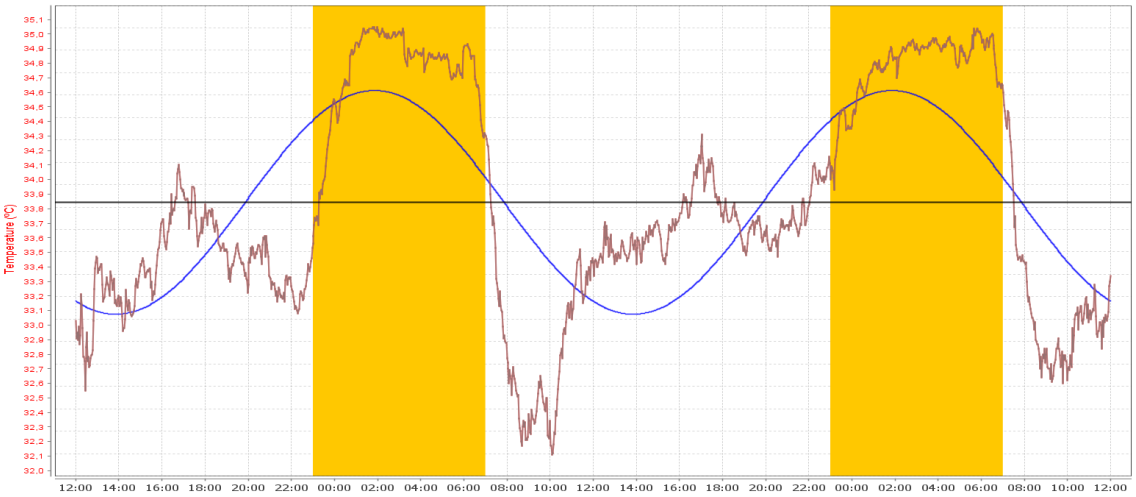
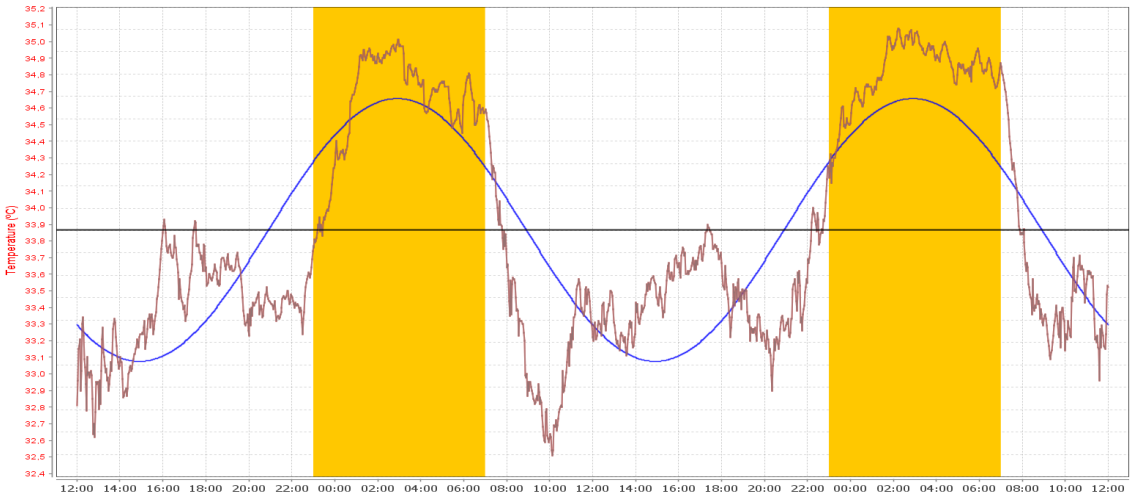


Figure 1. Distal skin temperature function and adjustment to cosinor of substance use disorder group (a) and substance use disorder with comorbid depression group (b). Colored area represents the sleep period.

a.



b.

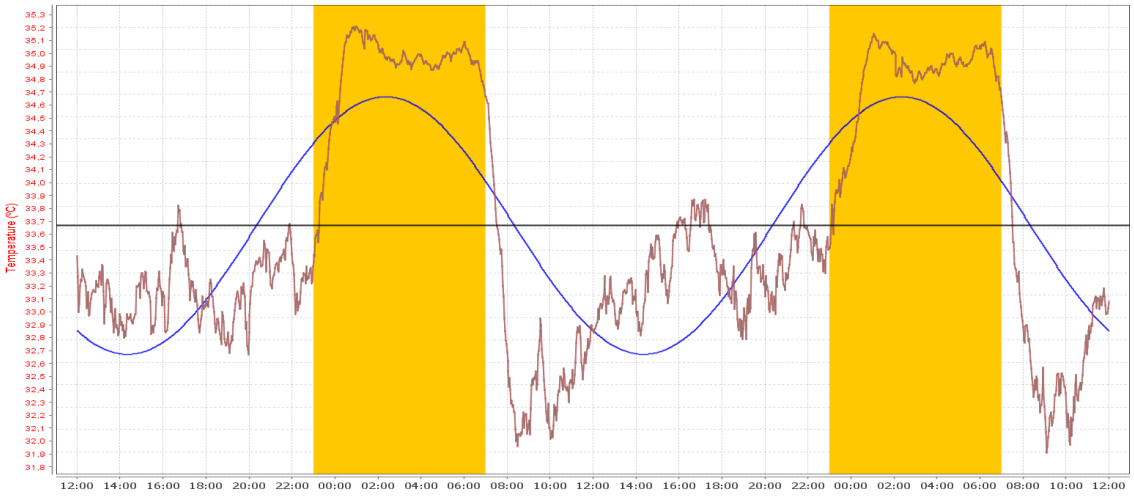


Figure 2. Distal skin temperature function and adjustment to cosinor of ambulatory group (a) and therapeutic community group (b). Colored area represents the sleep period.