UNIVERSITAT DE BARCELONA

Circadian functioning and quality of life in patients with and without dual disorders

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Circadian functioning and quality of life in substance use disorder patients with and without dual disorders

PhD Dissertation

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Dedicated with love to my dear
parents and siblings

“Learn from yesterday, live for today, hope for tomorrow. The important thing is not to stop questioning”

Albert Einstein

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This doctoral thesis is the result of the support, collaboration, and work of many more people, to whom I would like to thank as the author. The beginning of all this work presented here takes place in 2016. Dr. Ana Adan trusted me to do this research project as a dual pathology in Iran. We began to walk the path of the doctorate. Definitely, my completion of this project could not have been accomplished without her support. I would like to express my deep and sincere gratitude for doing this research. I am extremely grateful for her guidance, help, teachings, punctuality, empathy, accuracy, responsibility, and, above all, her patience. She taught me to rely on my own knowledge and to explore what I learned. Thank you Ana for all these. Throughout this long journey, I learned to extend my heartfelt thanks to my parents for their love, prayers, sacrifices for educating and preparing me for the future, and also many years of unconditional financial and emotional support despite the economic problems. They always helped me, taught me to be persistent and a fighter, and encouraged me to do what makes me happy. I want to thank all the patients who participated in this doctoral thesis. Finally, I wish also to thank the Specialist psychiatric center and Center of addiction treatment. In these centers, in addition to registering subjects for the sample, I have learned practical aspects of the management of patients with addictions and mental disorders and I have been in contact with different situations these patients go through during their treatment. I want to thank all the professionals at these centers especially distinguished managers of both centers for their collaboration and for their time.

Thanks to each and every one of you for accompanying me on this path and I wish you all the best.

Iman

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ABSTRACT

Sleep is a critical part of the individual's daily performance and survival that is part of the primary sleep-wake circadian rhythm. Any sleep disturbance causes damage to wakefulness (fatigue, drowsiness) and can even lead to various health problems. The alteration of the circadian rhythm affects the quality of sleep, decreases the quality of life (QOL) and can motivate the development of various medical, neurological and mental pathologies such as major depressive disorder (MDD) and substance use disorder (SUD)

The relationship between social time and endogenous rhythms is an individual difference called chronotype that classifies individuals into morning type, intermediate or no type, and evening type. There are numerous studies that point to the evening type as a risk factor for developing maladaptive behaviors, sleep disorders, psychiatric symptoms and mental disorders, among which SUD and MDD stand out. Substance use and sleep problems are mutual and feed off each other. Substance use influences sleep with detrimental effects, and the presence of a sleep problem can promote substance use as an attempt at self-medication. Although the available evidence on circadian rhythm, chronotype and SUD in the Iranian population is very limited, existing studies indicate a high prevalence of self-medication with the risk of entering a vicious cycle and developing both SUD and a more serious sleep problem. Substance use can also cause mental illness and vice versa. The presence of a mental disorder comorbid with SUD, which we refer to as dual pathology (DP), implies more clinical (hospitalizations, suicide attempt, relapses) and social problems compared to the presence of a single disorder. However, there is little research in this area and even less in the study of the affectation of circadian rhythmicity and QOL in patients with DP.

The general objective of this study was to investigate the clinical characteristics and differences, circadian functioning and QOL in a sample of 238 Iranian male patients (38.14 ± 10.11 years) under treatment with a diagnosis of SUD (N = 81), with SUD and comorbid schizophrenia (SUD + SZ; N = 75) and with SUD and comorbid major depressive disorder (SUD + MDD; N = 82). Another objective was to create the Persian version of the Sleep Belief Scale (SBS) and explore its psychometric properties in the sample of patients studied. The history and presence of clinical symptoms were assessed together with circadian functioning, using various standardized

instruments [hourly parameters for social jet-lag (SJL), the reduced morning-evening questionnaire (rMEQ), the Pittsburgh sleep quality index (PSQI) and SBS]. For QOL the scale developed by the World Health Organization (WHOQOL-BREF) was used. This study is the first investigation with clinical diagnoses and selected measurements developed in Iran.

According to the sociodemographic and clinical variables, the SUD + SZ patients were much younger single people, with a higher number of substance use and an earlier age of onset of SUD compared to the other two groups. In the SUD + MDD group, there was more concomitance of organic pathology, a greater number of antecedents of psychiatric disorders and suicide attempts, as well as more illiterate individuals. SUD patients contributed the highest proportion of opium and crystal users. Both the SUD and SUD + SZ groups had a higher proportion of heroin users and polydrug users.

Regarding sleep characteristics, although no differences were observed between the groups in the SJL, the SUD patients tended to go to bed later than the DP groups both during working days and on days off (weekend) together with a greater presence of IT. In contrast, patients with SUD + MDD were more prone to the morning type and patients with SUD + SZ to the evening type. In the total sample of our study, the evening patients were those who showed the highest rate of polydrug users.

The SUD + MDD group had the worst PSQI scores, even after controlling for age and age of onset of SUD, in addition to showing a greater number of drug prescriptions for sleep. In contrast, the SUD + SZ group was the one that showed the worst scores in the sleep disturbance parameter of the three. The age of onset of SUD and the severity of MDD showed a negative and positive relationship, respectively, with the total scores of the PSQI. Furthermore, since we did not find any interaction between the chronotype and the groups with respect to sleep quality, once the mental disorder has developed, it and its severity seem to be the best indicators of sleep disturbances, regardless of the patient's chronotype .

The SBS in its original form did not show adequate psychometric properties in the patient sample, with unweighted items in any dimension and an internal reliability of less than 0.700. A reduced version with 13 items was created, which meets the minimum reliability criteria and requires less

response time. The analyzes carried out with both the original proposal and our reduced one provided better scores for the SUD and SUD+MDD groups in both cases compared to the SUD + SZ group. This study highlights that a higher number of substance use and the greater severity of SZ or MDD are linked to poorer scores on the SBS, both on the original scale and on the reduced scale. Taking into account the dimensions of SBS (original and reduced), the severity of SZ was negatively related to the scores of Behaviors incompatible with sleep and Thoughts and attitudes towards sleep, while the number of substance use was negatively associated with the scores. Behaviors incompatible with sleep. In addition, in the SUD + MDD group, lower scores in Thoughts and attitudes towards sleep were related to a higher number of substance use, a lower age of onset of SUD and greater severity of MDD.

The SUD group provided a better QOL than the DP groups in all dimensions, even after controlling for confounding factors. Except for Environmental Health in the SUD group, all QOL scores in the three groups were lower than the normative data for the healthy population. In the total sample, we found that the number of substance use was negatively related to the overall QOL score. In the SUD + SZ group, more suicide attempts and more SJL were associated with less Physical Health and Social Relationship. On the other hand, in the SUD + MDD group, the higher the SJL and the severity of MDD, the worse physical health was observed and the lower sleep latency was related to more mental health.

Our results indicate that DP patients in most clinical and circadian characteristics –with an emphasis on sleep-, as well as QOL suffer more problems compared to patients with SUD. This highlights the importance of caring for these patients in treatment centers for those variables that may be modified during the therapeutic process. Future studies may consider our results for the promotion of knowledge in this area, with the aim of better understanding the associations between variables and overcoming the limitations of the present work with the ultimate aim of designing better and more effective treatments.

RESUMEN

El sueño es una parte fundamental del desempeño diario y la supervivencia del individuo que forma parte del ritmo circadiano principal de sueño-vigilia. Cualquier alteración del sueño provoca un perjuicio para la vigilia (fatiga, somnolencia) e incluso puede derivar en diversos problemas de salud. La alteración del ritmo circadiano afecta la calidad del sueño, disminuye la calidad de vida (CV) y puede motivar el desarrollo de diversas patologías médicas, neurológicas y mentales como el trastorno depresivo mayor (TDM) y el trastorno por uso de sustancias (TUS).

La relación entre el tiempo social y los ritmos endógenos es una diferencia individual denominada cronotipo que clasifica a los individuos en tipo matutino, intermedio o ningún tipo y tipo vespertino. Existen numerosos estudios que apuntan al tipo vespertino como factor de riesgo para desarrollar conductas inadaptadas, trastornos del sueño, síntomas psiquiátricos y trastornos mentales, entre los que destacan el TUS y el TDM. El uso de sustancias y los problemas de sueño son mutuos y se retroalimentan. El uso de sustancias influye en el sueño con efectos perjudiciales y la presencia de un problema de sueño puede promover el consumo de sustancias como un intento de automedicación. Aunque la evidencia disponible sobre ritmo circadiano, cronotipo y TUS en la población iraní es muy limitada, los estudios existentes indican una alta prevalencia de automedicación con el riesgo de entrar en un círculo vicioso y desarrollar tanto TUS como un problema de sueño más graves. El uso de sustancias también puede causar enfermedades mentales y viceversa. La presencia de un trastorno mental comórbido con TUS, al que nos referimos como patología dual (PD), implica más problemas clínicos (hospitalizaciones, intento de suicidio, recaídas) y sociales en comparación con la presencia de un solo trastorno. Sin embargo, hay poca investigación en esta área y menos todavía en el estudio de la afectación de la ritmicidad circadiana y la CV de los pacientes con PD.

El objetivo general de este estudio fue el de investigar las características y diferencias clínicas, el funcionamiento circadiano y la CV en una muestra de 238 pacientes varones iraníes (38,14 ± 10,11 años) en tratamiento con diagnóstico de TUS (N = 81), con TUS y esquizofrenia comórbida (TUS+SZ; N = 75) y con TUS y trastorno depresivo mayor comórbido (TUS+TDM; N = 82). Otro objetivo fue crear la versión persa de la *Sleep Belief Scale* (SBS) y explorar sus propiedades psicométricas en la muestra de pacientes estudiados. El historial y la presencia de síntomas clínicos

se evaluaron junto con el funcionamiento circadiano, mediante diversos instrumentos estandarizados [parámetros horarios para el jet-lag social (JLS), el cuestionario reducido de matutinidad-vespertinidad (rMEQ), el índice de calidad del sueño de Pittsburgh (PSQI) y la SBS]. Para la CV se utilizó la escala desarrollada por la Organización Mundial de la Salud (WHOQOL-BREF). Este estudio es la primera investigación con los diagnósticos clínicos y mediciones seleccionadas desarrollado en Irán.

Según las variables sociodemográficas y clínicas, los pacientes TUS+SZ eran personas solteras mucho más jóvenes, con un mayor número de consumo de sustancias y una edad más temprana de inicio del TUS en comparación a los otros dos grupos. En el grupo SUD+TDM se observó más concomitancia de patología orgánica, una mayor cantidad de antecedentes de trastornos psiquiátricos e intentos de suicidio, así como más individuos analfabetos. Los pacientes TUS aportaron la mayor proporción de consumidores de opio y cristal, mientras que los SUD+SZ mostraron la tasa más alta de número de sustancias consumidas. Tanto el grupo SUD como el SUD+SZ tenían una mayor proporción de consumidores de heroína y de policonsumidores.

En cuanto a las características del sueño, si bien no se observaron diferencias entre los grupos en el JLS, los pacientes TUS tendían a una hora más tardía de acostarse que los grupos PD tanto durante los días laborales como en los días libres (fin de semana) junto a una mayor presencia del TI. En cambio, los pacientes con TUS+TDM eran más propensos al tipo matutino y los pacientes con TUS+SZ al tipo vespertino. En la muestra total de nuestro estudio, los pacientes vespertinos fueron los que mostraron la tasa más alta de policonsumidores.

El grupo TUS+TDM aportó las peores puntuaciones del PSQI, incluso después de controlar la edad y la edad de inicio del TUS, además de mostrar una mayor cantidad de prescripciones farmacológicas para dormir. En cambio, el grupo SUD+SZ fue de los tres el que mostró las peores puntuaciones en el parámetro de alteración del sueño. La edad de inicio del TUS y la gravedad del TDM mostraron una relación negativa y positiva, respectivamente, con las puntuaciones totales del PSQI. Además, dado que no encontramos ninguna interacción entre la cronotipo y los grupos con respecto a la calidad del sueño, una vez desarrollado el trastorno mental éste y su severidad parecen ser los mejores indicadores de las alteraciones del sueño, con independencia de la cronotipo del paciente.

La SBS en su forma original no mostró unas propiedades psicométricas adecuadas en la muestra de pacientes, con ítems sin ponderar en ninguna dimensión y una fiabilidad interna inferior a 0,700. Se creó una versión reducida con 13 ítems, que cumple con el mínimo criterio de fiabilidad y requiere menor tiempo de respuesta. Los análisis realizados tanto con la propuesta original como con la nuestra reducida aportaron en ambos casos mejores puntuaciones de los grupos TUS y TUS+TDM en comparación con el grupo TUS+SZ. Este estudio destaca que un mayor número de uso de sustancias y la mayor gravedad de SZ o MDD se vinculan a peores puntuaciones en la SBS, tanto en la escala original como en la reducida. Teniendo en cuenta las dimensiones de SBS (original y reducida), la gravedad de SZ se relacionó negativamente con las puntuaciones de Comportamientos incompatibles con el sueño y Pensamientos y actitudes hacia el sueño, mientras que el número de consumo de sustancias se asoció negativamente con los Comportamientos incompatibles con el sueño. Además, en el grupo TUS+TDM las puntuaciones más bajas en Pensamientos y actitudes hacia el sueño se relacionaron con un mayor número de consumo de sustancias, menor edad de inicio del TUS y mayor gravedad del TDM.

El grupo SUD aportó una mejor CV que los grupos con PD en todas las dimensiones, incluso tras controlar los factores de confusión. A excepción de la Salud ambiental en el grupo TUS, todas las puntuaciones de CV en los tres grupos fueron inferiores a los datos normativos de la población sana. En la muestra total, encontramos que el número de consumo de sustancias se relacionó negativamente con la puntuación general de CV. En el grupo TUS+SZ, más intentos de suicidio y más SJL se asociaron a una menos Salud física y Relación social. En cambio, en el grupo TUS+TDM, a mayor JLS y gravedad del TDM se observó peor Salud física y la menor latencia del sueño se relacionaba con más Salud psíquica.

Nuestros resultados indican que los pacientes con PD en la mayoría de las características clínicas y circadianas –con énfasis en el sueño-, así como la CV sufren más problemas en comparación con los pacientes con TUS. Ello resalta la importancia de la atención a estos pacientes en los centros de tratamiento de aquellas variables que puedan ser modificadas durante el proceso terapéutico. Los estudios futuros pueden considerar nuestros resultados para la promoción del conocimiento en este ámbito, con el objetivo de comprender mejor las asociaciones entre variables y superar las limitaciones del presente trabajo con la finalidad última de diseñar tratamientos mejores y más efectivos.

LIST OF ABBREVIATIONS

AAP: American academy of pediatrics

ADHD: Attention deficit hyperactivity

AFFM: Five factor model of personality

APA: American psychiatric association

BART: Analogue risk task

BD: Bipolar disorder

BDI: Beck depression inventory

BTF: Bedtimes on free days

BTW: Bedtimes on workdays

CBT: Cognitive behavior therapy

CBT-I: Cognitive behavior therapy for insomnia

CD: Circadian disruption/disturbance

CM: Contingency management

CR: Circadian rhythm

CSM: Composite scale of morningness

CT: Circadian typology

DD: Dual disorder

DP: Dual pathology

DST: Distal skin temperature

DSM-5: Diagnostic and statistical manual of mental disorders. Fifth version

DSM IV-TR: Diagnostic and statistical manual of mental disorders. Fourth edition-revised

EEG: Electroencephalographic

ESS: Epworth sleepiness scale

ET: Evening type

HAMD-17: Hamilton depression rating scale-17

HIV: Human immunodeficiency virus

IAPS: Iranian addiction potential scale

IT: Intermediate type

MBSR: Mindfulness-based stress reduction

MCTQ: Munich chronotype questionnaire

MDD: Major depressive disorder

MESSI: Morningness-eveningness-stability-scale improved

MINI: International neuropsychiatric interview

MSW: Mid-sleep on workdays

MSF: Mid-sleep on free days

MH: Mental hospital center

MHECA: Mental health epidemiologic catchment area

MI: Motivational interviewing

MT: Morning type

MTF: Monitoring the future

NFSAP: National foundation sleep in America poll

NEO-30: Neuroticism-extraversion-openness inventory-30

NIDA: National institute on drug abuse

NIH: National institutes of health

NIMH: National institute of mental health

NSDUH: National survey on drug use and health

OCD: Obsessive Compulsive Disorder

PANAS: Positive and negative affect schedule

PANSS: Positive and negative syndrome scale for schizophrenia

PSQI: Pittsburgh sleep quality index

PTSD: Posttraumatic stress disorder

Q-LES-QSF: Quality of life enjoyment and satisfaction questionnaire

QOL: Quality of life

RAR: Rapid assessment response

REM: Rapid eye movement

rMEQ: Reduced morningness-eveningness questionnaire

SAD: Seasonal affective disorder

SAMHSA: Substance abuse and mental health services administration

SBS: Sleep beliefs scale

SCID: Structured clinical interview for DSM disorders

SP: Sleep problem

SJL: Social jet-lag

SQN: Suprachiasmatic nucleus

SUD: Substance use disorder

SUD+MDD: Substance use disorder comorbid major depressive disorder

SUD+SZ: Substance use disorder comorbid schizophrenia

SUMS: Shiraz University of medical sciences

SZ: Schizophrenia

UNODC: United Nations office on drugs and crime

USWRS: University of social welfare and rehabilitation science

WHO: World health organization

WUW: Wake up during the workdays

WUF: Wake up during the free days

ZKPQ: Zuckerman-Kuhlman personality questionnaire

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1. INTRODUCTION

1.1. Circadian rhythms

Earth's rotation around its axis creates a day and night cycle, which influences physiological and psychological variations in flora and fauna (Roenneberg et al., 2007; Kooij & Bijlenga, 2013). The main biological cycles of the human body include circadian (24h), circamensual (28 days), and circannual rhythm (a year/ 365 days). Daily, monthly, and yearly variations in the environment are correlated with the Earth's spin and motion (Oginska & Oginska-Bruchal, 2014). The circadian rhythms (CR) of the human body, which is also replicated about every 24 h (Hasler et al., 2015; Steven et al., 2016), is the most studied subject due to its robustness as well as practical and clinical interest in this scope. The word circadian is derived from a Latin word, with "circa" meaning about and "diem" meaning a day (Jagannath & Foster, 2013; Kooij & Bijlenga, 2013).

CRs are determined by the master clock or suprachiasmatic nucleus (SQN), which is located in the anterior hypothalamus (Dallaspezia et al., 2011; Li et al., 2013; Li, 2014; Schnell et al., 2014; Rosenvasser et al., 2015), and made up of about 20,000 neurons (Liu & Chung, 2015). Irrespective of external lighting or external indicators, CR works for 24 h (Rahimi & Ebrahimi, 2016). Moreover, despite the difficulties in chronological and social cues, the human body still displays daily cycles of the sleep-wake (Monteleone & Maj, 2008; Roenneberg & Merrow, 2016). Distinctions between CR in individuals also pertain to parental care rhythms and environmental circumstances (Batinga et al., 2015). The reason is that CR slowly but surely enhances its extent after childbirth, and caregivers' entrainment has an important role in its synchronizing (Brooks & Canal, 2013). Accordingly, the circadian system is active and resilient (Liu & Chung, 2015). Most of the physiological and behavioral processes reveal CRs (Roenneberg et al., 2007; Yong et al., 2016). Among these processes, some have been recognized as biological markers including the core body temperature (Adan et al., 2012), sleep-wake-cycle (Bootzin & Stevens, 2005; Konttinen et al., 2014), cortisol (Jagannath et al., 2013), and melatonin hormones (Selvi et al., 2011; Roeser et al., 2013; Doi et al., 2015).

In mammals, light is a pivotal environmental element that assists the biological clock to adapt to the environment (Roenneberg et al., 2007; Brooks & Canal, 2013). Light moderates the arousal structures of the brain by increasing the levels of light alertness and reducing sleep latency (Wulff et al., 2010). Being able to detect and reply to environmental light is the first step for developing CR to synchronize the surrounding light. So, early light in the environment has the main effect on the circadian system (Khodapanahi, 2012).

In the last century, with the initiation of using electrical lights and increased social demands, human sleep forms have been changed significantly (Carissimi et al., 2016). Temporal stimulators in the environment are known as zeitgeber or time givers, as they are crucial components for synchronizing the endogenous CR with the 24-h day (Roenneberg et al., 2007). The zeitgeber is a German word meaning a rhythmically occurring natural phenomenon that acts as a cue in the regulation of the body's circadian rhythms. However, the social rhythms such as artificial light, social activity (Ritter et al., 2011; Baron & Reid, 2014; Kooij & Bijlenga, 2013; Carissimi et al., 2016), and nutritional behavior (Togo et al., 2017) are relevant zeitgebers for human. The main zeitgeber is the daily oscillation in light and dark (Roenneberg et al., 2007). For example, as an exogenous factor, nocturnal activities (Asarnow et al., 2014) and mealtime, as an important socio-environmental synchronizer (Levandovski et al., 2013), have been postulated effective in entraining the circadian system. Besides, it has been revealed that higher quality of social rhythms is related to a better quality of sleep and mental issues such as depressive symptoms (Monteleone et al., 2011; Friborg et al., 2014).

Behavior is usually accommodated by the light/dark cycle (Khodapanahi, 2012) and the light/dark cycle has the most important role in time givers (Hasler et al., 2015). Thus, the existence of a light-sensitive mechanism is imperative in the human body. The light/dark cycle is detected by retinal (rod and conic) photoreceptors (Jagannath et al., 2013) and light can synchronize the master clock by being received via the retina and retinoic hypothalamic field (Dallaspezia & Benedetti, 2011; Hickie et al., 2013; Schnell, 2014). Figure 1 shows the effective markers on the circadian system and zeitgeber entrainments.

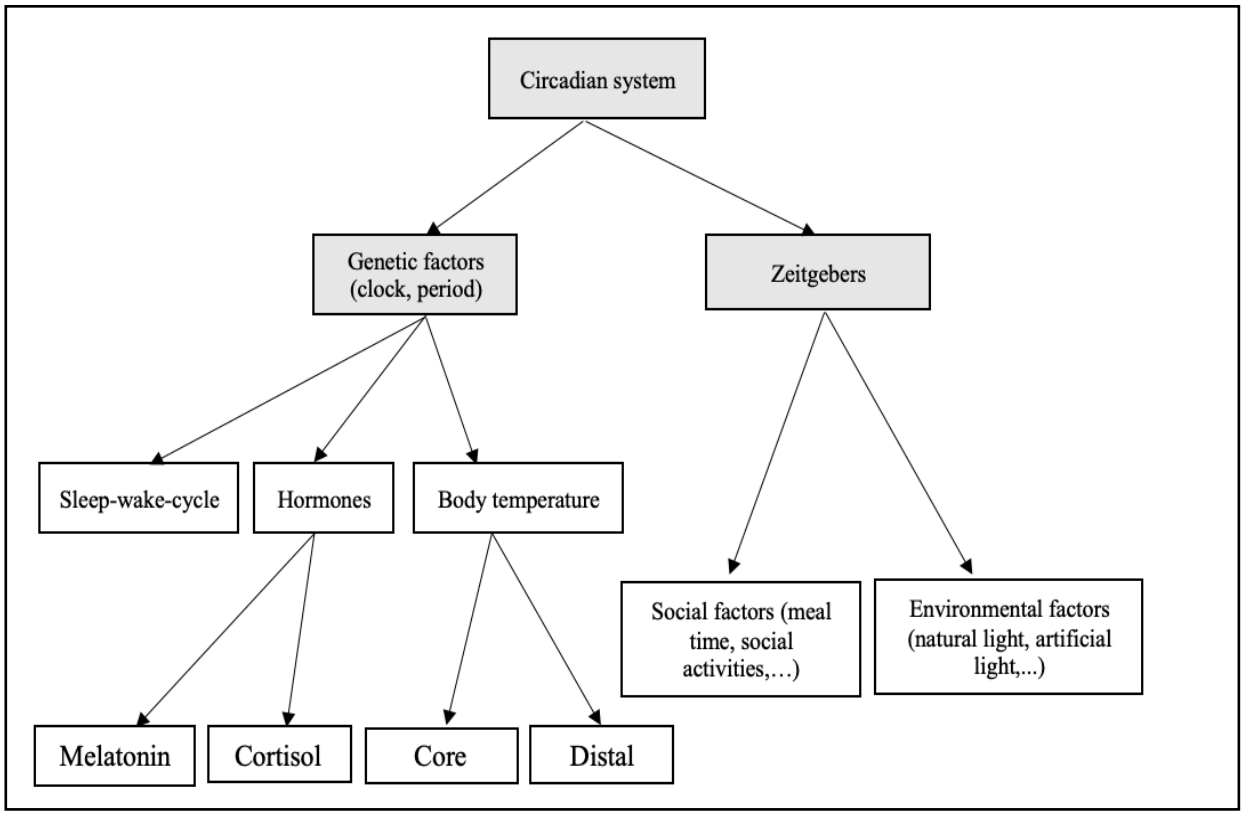


Figure 1. The effective markers of circadian system and zeitgebers entrainments.

The sleep-wake rhythmicity typically develops during the first three months of life, depending on the duration of light exposure and maternal factors (Reppert & Schwarts, 1983; Gallaher et al., 2018). Retinal light exposure in the night postpones the timing of the clock; while, light exposure later in the night and early in the morning enhances the timing of the clock. Even tiny alterations in normal light exposure during the late evening hours can considerably affect both plasma melatonin secretion and the entrained phase of the human CRs (Asarnow et al., 2014). It is of note that light and melatonin (sleep hormone) have opposite phase-shifting effects. Contact with light phase advances or phase delays the sleep-wake-cycle, depending on the timing, power, and duration of light exposure (Barion, 2011; Kooij & Bijlenga, 2013). For example, evening light can interrupt the circadian phase (Figueiro et al., 2014; Bartel et al., 2015). It has been suggested that distal skin temperature (DST) could be used to predict the internal phase instead of the onset of melatonin secretion (Bonmati-Carrion et al., 2014) and even as a marker in response to treatment of addicted patients (Capella et al., 2018).

In recent decades, it has been reported that SQN also receives non-photic input from different parts of the brain (Gradin et al., 2006). Social signals such as the timing of social interplays, mealtime (Wulff et al., 2010), and exercise are principal non-photic indications (Asarnow et al., 2014). These social signals, in turn, can also alter our biological clock to an early or late pattern. The non-photic inputs and photic-dependent signals have reverse effects on the level of SQN. Outputs of SQN affect the regulatory systems, which happen primarily in the brain or other major physiological structures (Hickie et al., 2013). As mentioned above, due to the internal biological clock, the master clock is sensitive to changes especially alternations in the light-dark cycle. Therefore, when the master clock is confronted with perturbations, many-body physiological interactions synchronized with cycle and several interplays (melatonin secretion and core body temperature) cannot adapt simply. In such a case, biological cycle disorders may appear (Khodapanahi, 2012). For instance, alternation of CR caused by lack of night sleep leads to loss of peak of melatonin secretion and reduction in body temperature at night, impairing the quality of sleep (Adan, 2013). Figure 2 presents the localization and environment inputs of SQN in the human brain.

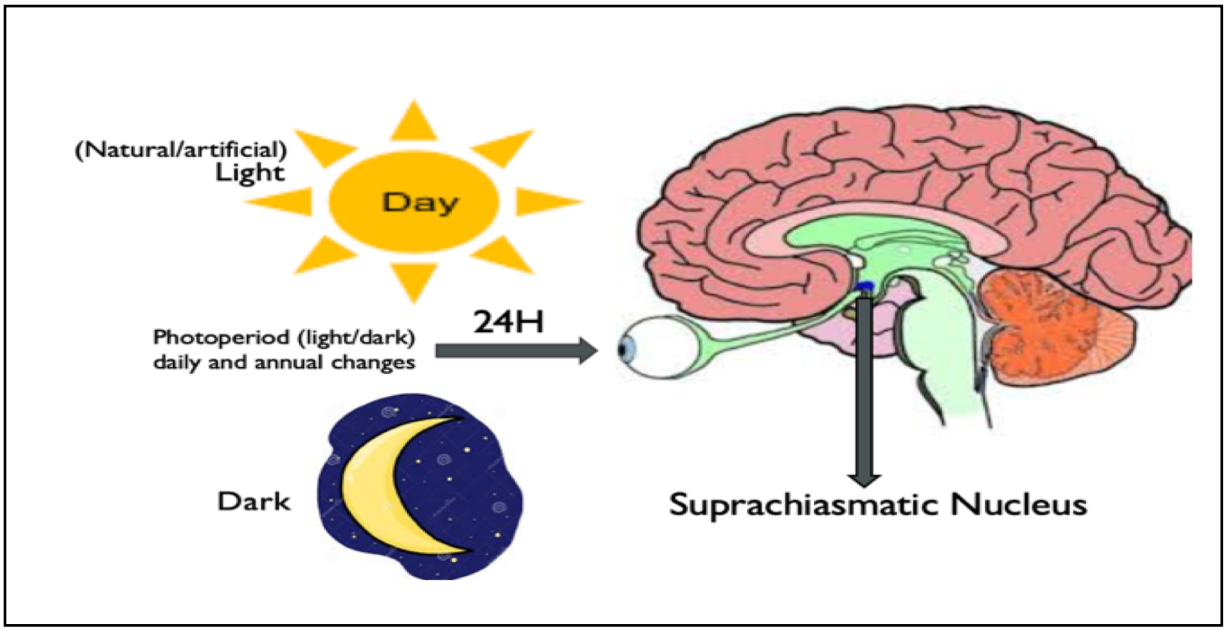


Figure 2. Suprachiasmatic nucleus (SQN) in human's brain and connection with light-dark environment signals.

In Schnell, Albrecht, and Sandrelli's model (2014), an interaction among genes and the environment might also cause a misalignment in the circadian system in vulnerable individuals. Misalignments can be categorized as temporary such as time zone travel or jet-lag, which is the difference between biological and environmental/social rhythms (Antypa et al., 2016), and chronic such as individuals' preferences for sleep-wake timing (Baron & Reid, 2014). Circadian clock also can readapt to the new daily program, with a mean level of 1 day per each hour of time zone slowly (Schnell et al., 2014). One of the best examples of disrupted light/dark cycles in humans is seasonal affective disorder (SAD) or winter depression. Due to SAD, a depressive episode usually happens in winter or fall when light exposure is lowermost, and spontaneously recovers in spring or summer when light exposure is in a higher range (Wulff et al., 2010; Asarnow et al., 2014). Figure 3 shows the synchronizing effect of variation in photoperiod on the circadian and annual rhythms in the daily clock.

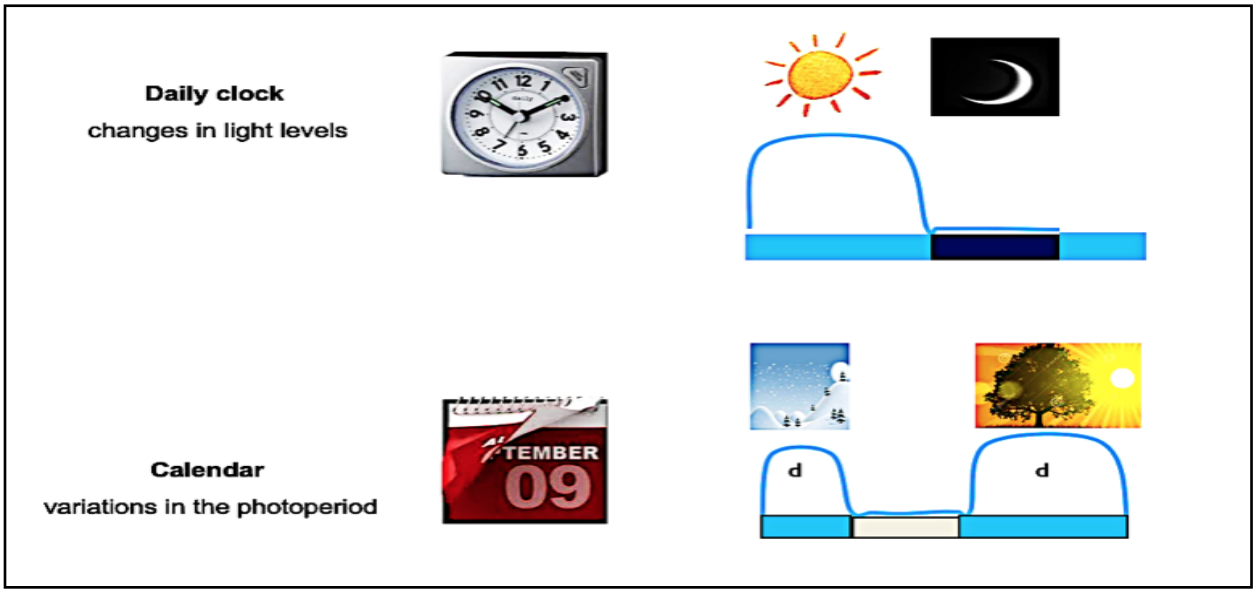


Figure 3. The synchronizer effect of photoperiod in the circadian and annual rhythms.

1.2. The sleep-wake-cycle as a marker of circadian rhythms

Sleep is a critical part of the everyday performance (Bartel et al., 2015). The main aim of sleep is development and recovery of the brain (Telzer et al., 2015; Tochigi et al., 2016), especially for having better mental and physical diurnal state (Lund et al., 2010; Shochat et al., 2014; Minges & Redeker, 2016). Ideal sleep quality is attained when the required sleep time is in orientation with the time of the endogenous CR of sleep and wake tendency (Barion, 2011). Sleep is characterized by poor responsiveness to external stimuli (Wulff et al., 2010) as a recovery procedure, an adaptive action, incorporating resonance of immune system, growth, metabolic processes, and memory stabilization (Zanini et al., 2015). In the last few years, a growing interest has appeared in sleep and its activities.

Sleep a fundamental survival element, a compound activity, and an apparent interplay between neurotransmitters, hormones, and the day/night cycle (Di Milia et al., 2005; Hickie et al., 2013). Indeed, it is the production of an interplay between neurotransmitters and multiple brain centers. This process is synchronized by the action of sleep-promoting neurons in the anterior hypothalamus and sleep-inhibiting neurons in the lateral and posterior hypothalamus on the arousal-promoting systems in the brainstem. Any irregularity in the neurotransmitter system affects the sleep/circadian procedures (Wulff et al., 2010; Pritchet et al., 2012; Jagannath et al., 2013). The CR and sleep interact and balance each other to achieve the best daily behavioral cycle, metabolism, and physiology in one's body (Hurley et al., 2016).

The switch between wake to sleep is determined by specific brain regions, especially the basal forebrain (Wulff et al., 2010). Sleep is linked with an expansive range of emotional, cognitive, and somatic indications (Jagannath et al., 2013). However, there is limited knowledge of sleep quality and its effects on emotion managing (Gobin et al., 2015). Studies on patients emphasize the importance of a robust and regular CR to recovery and stay healthy (Ortiz-Tudela et al., 2010).

Sleep hygiene is a list of simple routine measures that have been confirmed to have a significant effect on improving nights' rest. These include reducing alcohol and caffeine use, avoiding television watch, and or browsing social media late in the evening (Kooij & Bijlenga, 2013). Adequate sleep is important for physiological performance and the timing of sleep is necessary for

social demands (Vollmer et al., 2013). Sleep plays an important role in the optimal cognitive process and cardiovascular health (Klingaman et al., 2015). In the case of adolescents, this adequate sleep is positively associated with a healthier diet, physical exercise, better stress management, life thankfulness, and being less prone to obesity (Shochat et al., 2014). Recently, a large study on 804 adolescents suggests that families can create better sleep hygiene by encouraging teens to go to bed on time, establishing earlier and more steady sleep-wake up times, and limiting both electronic media and caffeine use in the evening (Feliciano et al., 2019).

Conservation and connection of the body's daily schedule and its synchronization with the light-dark cycle are among the responsibilities of the endogenous clock (Levandovski et al., 2011). Coordination between endogenous circadian fluctuations (i.e., metabolic, physiological, or behavioral processes) and social indications (i.e., zeitgebers and working hours) seem essential for physical and mental health, especially sleep (Müller et al., 2016b; Carvalho et al., 2018). Three drivers control duration, efficiency, and quality of sleep. Endogenous drivers are the circadian system and homeostatic hourglass oscillator or homeostatic sleep pressure without being affected by seasons (Friborg et al., 2014). Second one is exogenous or socially structured (school and work times). The homeostatic system that disappears during sleep increase the pressure to sleep with each waking minute. Meanwhile, the circadian system raises the patterns of alertness/sleepiness during a 24-hour rhythm (Haraden et al., 2017). These aspects of sleep are related and overlapping but are generated autonomously (Asarnow et al., 2014). Also, all of them can directly affect one's mood and mental health (Di Milia et al., 2005).

After the report of the American Academy of Pediatrics on extreme sleepiness in adolescents in 2005, and recognized inadequate sleep in adolescents as a serious health peril in 2010 in American Medical Association, a plethora of articles were published about sleep problems (SPs) (Owens, 2014). Moreover, recently night shift workers have been categorized as risk factors by the International Agency for Investigation on Cancer (Papantoniou, et al., 2015). Sleep is among the most recurrent health complaints in adults, and about one out of four has a problem related to sleep; hence, in the general population, management of sleep is required (Soldatos et al., 2005; Adan et al., 2006).

In 1985, Lynn Farr used the term circadian disruption (CD) for the first time and stated that it deeply affects sleep. The most important biological cycle disturbances appear in the form of sleep disorders (Khodapanahi, 2012). Moreover, one way to evaluate the CR problems is revealed in sleep-wake-cycles, which might be the greatest familiar circadian cycle (Jagannath et al., 2013). Small changes in brain function can have an enormous influence on sleep and disturbed sleep leads to several health problems (Pritchet et al., 2012). Self-remedy within drug can be considered an effort to ameliorate sleep and mood-related difficulties found with CD (Logan et al., 2014) although always fails in the medium and long term. Association between sleep and CR throughout the day is essential to combine sleep and wakefulness. Nevertheless, disturbance in this phase leads to fatigue or sleepiness (Asarnow et al., 2014). Also, it has been revealed that greater CD is associated with more severe illness and suicidality (Malhi & Kuiper, 2013; Bahk et al., 2014) and may even influence the choice of suicide methods (Selvi et al., 2011).

Both CD and SPs are initiated by a misalignment between the endogenous diurnal timing system and environmental rhythm (Afonso et al., 2014) such as homework, jobs, extracurricular activities, or use of technology (Boergers et al., 2014). However, the causal relationship between the two conditions, SP or problems in CRs, is not fully explicit (Li, 2013). One of the most important and impressive consequences of misalignment of the sleep-wake-cycle are SPs such as insomnia, difficulty in waking up in the morning, and drowsiness during the day, which are markers that lead to request meditation in sleep clinics (Baron & Reid, 2014). Tendencies, beliefs, and mental arousals are risk factors in SPs, and all play an important role in the preservation of sleep (Jefferson et al., 2005; Bartel et al., 2015).

Sleep regularity is a chief matter for functional levels of the central nervous system and behavioral level (Díaz-Morales & Escribano, 2015). Also, these behavioral and social agents play the main role in SPs and CDs (Afonso et al., 2014). Among these agents, we can include awakening and rising from bed, light exposure, exercise, social behaviors, eating habits, and nighttime activity (Hickie et al., 2013). Among the sleep-wake problems, insomnia and hypersomnia are the major sleep-wake disorders (Liu & Chung, 2015).

In terms of genetics, several studies have emphasized the importance of melatonin secretion in the onset and maintenance of sleep (Monti et al., 2013). Melatonin (or sleep hormone) is an intrinsic

hormone mainly generated in the pineal gland and plays an important role in regulating CRs (Wilson et al., 2010; Kooij & Bijlenga, 2013) and circadian typology (CT) (Oginska & Oginska-Bruchal, 2014). Melatonin secretion rises during the evening and provokes drowsiness, reduction of alertness, and decline of both body temperature and cardiovascular activity (Friborg et al., 2014). In this regard, melatonin has been considered the best predictor for sleep beginning (Adan et al., 2012; Friborg et al., 2014).

Moreover, during the 1970s and 1980s, researchers such as Papousek, Wehr, and Wirz-Justice emphasized the links between CR disturbance, sleep timing, and mental health (see for a revision of Wulff et al., 2010). CR synchronization associates with an individual's adjustment and variety of physical and mental activities (Goldstein et al., 2007; Carvalho et al., 2018). Hence, desynchronization of CRs may play an important function in the increase of health problems (Adan et al., 2012; Vetter et al., 2015; Carvalho et al., 2018) including cognitive functions such as attention, memory, and thinking style, which increase the accidents and damage (Meyrer et al., 2009; Hasler et al., 2013; Shochat et al., 2014). In recent years, the link between CD and several types of cancer (Smolensky et al., 2016; Wilson et al., 2019) and cardiovascular disorders (Anwar & White, 1998) has been observed. In addition to sleep disorders, the CD affects the development of psychiatric disorders (Park et al., 2015) such as major depressive disorder (MDD) (Wilson et al., 2019), anxiety (Allebrandt et al., 2014; Friborg et al., 2014; Bartel et al., 2015; Miller et al., 2015), bipolar disorders (BDs) (Smolensky et al., 2016), and substance use disorder (SUD) (Tochigi et al., 2016). Neurological pathologies like Parkinson's and Alzheimer's disease (Wulff et al., 2010) or multiple sclerosis (Najafi et al., 2010) have also been linked with CD. The relationship between disturbance in CR and the development of several relevant disorders is shown in Figure 4.

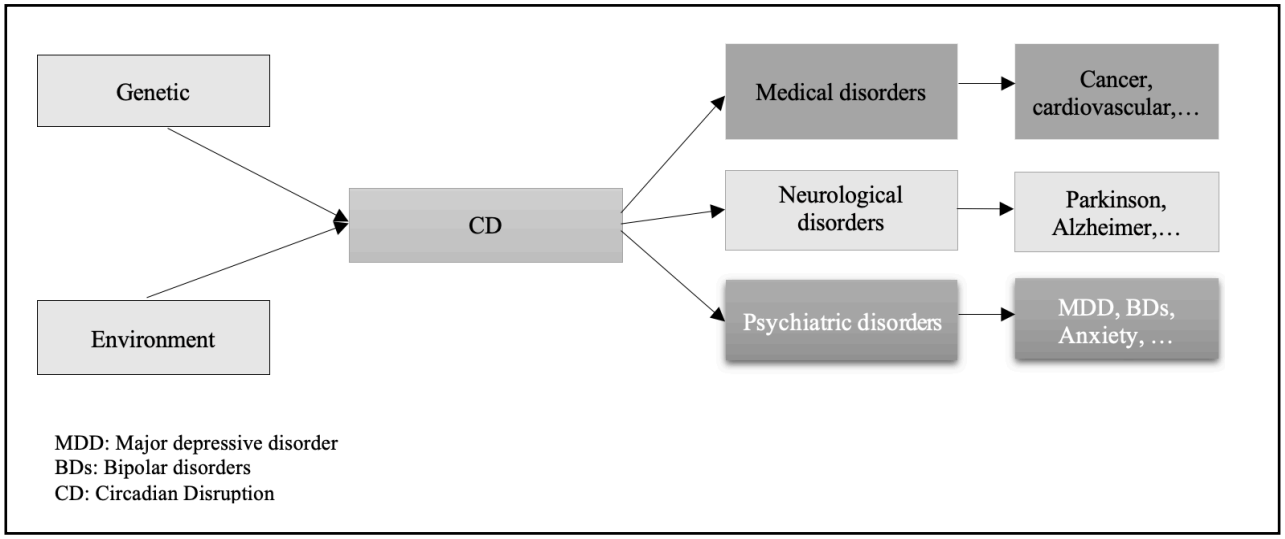


Figure 4. Disturbance in circadian rhythm (CR) and relevant disorders.

1.3. Circadian Typology

The nature of human social interactions leads to the addition of social time to the circadian clock, which plays an important role in our vast daily habits (Roenneberg et al., 2007). The relationship between this social time and the endogenous rhythms is a personal differential trait, which is known as a chronotype (CT) (Roenneberg et al., 2007; Adan et al., 2012). This relationship is not stationary and may change throughout the lifespan due to interactions (Haraden et al., 2017) such as the current mood (Druiven et al., 2020). As mentioned earlier, this individual difference is related to the optimal time for physical and mental performance (Correa et al., 2014; Qu et al., 2015; Tavernier et al., 2015). CT indicates two main contributions of individual differences in adapting mood, behavior, and physiology, to annual and daily changes in the environment (Putilov, 2018). Theoretically, CT should reflect both the typical timing of the sleep-wake-cycle and chronological patterning of individuals' daily activities and feelings of alertness (Haraden et al., 2017). It is of note that attention to CT is quite new, although it has advanced quickly in the two last decades (Levandovski et al., 2013; Qu et al., 2015).

Based on CT, individuals are categorized as morning-type (MT), intermediate or neither-type (IT), and evening type (ET) (Dockray & Steptoe, 2011; Adan et al., 2012; Tavernier & Willoughby, 2014; Lee et al., 2016). CT implies a preference for timing of sleep and wake behaviors, advance

in the MT, and delay in the ET, and it is hypothesized to contribute to circadian misalignment in people (Gaspa-Barba et al., 2009; Correa et al., 2014). The adjustment between CT and time of the day is known as "synchrony effect" (May & Hasher, 1998, May et al., 2005), which means people with MT have better functioning in the morning in contrast to ETs people who do better functioning late in the day (Vollmer et al., 2013; Escribano & Díaz-Morales, 2014; Piffer et al., 2014; Arbabi et al., 2015). In other words, individuals who are more aware in the morning tend to act better in the morning (MT) than in the afternoon while those who are more vigilant in the evening (ET) tend to perform better in the afternoon or evening (Adan et al., 2012; Díaz-Morales & Escribano, 2013; Konttinen et al., 2014; Piffer et al., 2014; 2016). Several elements such as task trouble, age, and period can influence the synchrony effect (Correa et al., 2017). In sum, although the relation between synchrony effect and CTs have been discussed, limited work has been conducted on the quiddity of this relationship so far. Understanding this essential theme might help to improve public health (Van der Heijden et al., 2013).

MTs prefer to wake up early in the morning and find it hard to remain awake outside their usual bedtime. In comparison, ETs desire to fall asleep late and have difficulty waking up in the morning (Kang et al., 2015; Lee et al., 2016). Moreover, MTs generally eat and go to bed earlier than ETs on workdays and particularly on free days (Levandovski et al., 2013) and IT individuals tend to do their tasks between MT and ET times. Nevertheless, depending on the variable studied, they may present a mixed pattern between the extreme groups (Levandovski et al., 2013). ETs have a delay in their biological and behavioral patterns of 2 to 12 hours in comparison to MTs (Adan et al., 2010a) and show phase differences in the circadian system functioning of individuals (Levy & Schibler, 2007).

In addition to environmental factors such as geographic situations, the formation of CT is affected by seasonal variation and work schedules (Piffer et al., 2014; Ponzi et al., 2014), genetic factors (Barclay et al., 2011), and individual factors such as sex and age (Adan et al., 2002). For example, there were more MT in the east, north, and rural areas (Adan et al., 2012), and ET was more severe among adolescents (Díaz-Morales & Escribano, 2015). Regardless of the geographical region or cultural features, CT had a normal distribution in the adult general population (Levandovski et al., 2013). Therefore, the meaning of who is early and who is late will be very distinctive depending on their lifestyle and geographical location (Roenneberg, 2012).

The link between wake-up and sleep preference could indicate SPs and negative mood changes in individuals (Müller et al., 2016b). Therefore, several questionnaires have been designed to measure CTs that reveal the relevant characteristics of the CR. The reliability and validity of these self-questionnaires have been confirmed via a variety of sources (Preckel et al., 2013; Inomata et al., 2014; Jeong et al., 2015). A logical way to study CTs is to ask people for their usually preferred sleeping and waking habits (Müller et al., 2015). On this point, several questionnaires are used to assess the CT. Three of them that are widely used in the world have shown good psychometric properties including internal reliability and external validity (Di Milia et al., 2013; Randler et al., 2017). The MEQ (Morningess-Eveningness Questionnaire) developed by Horne and Östberg (1979) contains 19 items with reliability ranging from 0.77 to 0.86. The rMEQ (reduced Morningess-Eveningness Questionnaire), developed by Adan & Almirall (1991), contains only five items from MEQ and its reliability is between 0.69 and 0.83. Finally, the CSM (Composite Scale of Morningness) developed by Smith et al. (1989) is a 13-item questionnaire that is used in many countries with reliability ranging from 0.65 to 0.90.

CT accounts for differences in the phase of physiological and psychological CR (Preckel et al., 2013). These differences are related to preferences for undertaking actions and sleeping at certain times of day along with self-recognition as being MT or ET compared to other people (Correa et al., 2014; Jankowski, 2016). In controlled laboratory circumstances, ETs displayed later timing of physiological markers in circadian timing. This result demonstrates that CT is at least somewhat biologically driven (Hasler et al., 2013). MT and ET are partially inheritable and related to polymorphisms in clock genes (Konttinen et al., 2014; Jankowski, 2016). In other words, individual distinctions in CT are generally stable over time and display a reasonable degree of heritability (Adan et al., 2012; Van der Heijden et al., 2013; Maestripieri, 2014; Druiven et al., 2020). In a 23-years follow-up, baseline, and follow-up study on 567 male adults, it was observed that 65% MTs considered themselves at similar CT while only 34% of ETs reported the same (Broms et al., 2014). The data indicated that ET is more subject to change over time (Koskenvuo et al., 2007; Broms et al., 2014). This genetic background is also revealed in the hormonal index, heart rate, body temperature (Vollmer et al., 2014), and sleep quality (Rique et al., 2014). In this respect, Piffer (2010) has proposed an assumptive scenario stating that MT is perhaps an ancestral evolutionary condition for our species while ET may hold out the mating-associated fitness profits, suggesting that ETs may have grown by sexual selection.

ETs and MTs vary in their forms of light exposure to preserve stable entrainment to the 24-h day and environmental factors, such as family or work obligations, which must be taken into consideration in sleep time (Paine & Gander, 2016). The current data propose that individual distinctions between ET and MT affect biological and psychological performance, in both health and disorders. ETs, choose values endorsing their independence and more creativity, while MTs present a higher receipt to social principles like security, adaptation, and custom (Roeser et al., 2013).

1.3.1. Sex, age and personality influence

A wide range of research has been done on sex and age in the CT field, even if the first major study was conducted by Roenneberg et al. (2004). The survey on 25,000 individuals in Germany showed that children have MT and adolescents show more ET around the age of 20 years. As people grow older, a propensity to go to bed and wake up earlier or a tendency to MT appears (Adan et al., 2012; Levandovski et al., 2013; Preckel et al., 2013). Meanwhile, ET increases from 12 to 15-20 years.

In Finland, a study on 10,503 individuals (at the age range of 25-74) showed that with advancing the age, MT increases but ET decreases (Merikanto et al., 2015). Another epidemiological study by Roenneberg (2007) has shown that CT has a regular bell-shaped distribution that differs by age and sex, with young adults depicting more ET. These results are confirmed in similar studies regardless of the country (Kim et al., 2010; Levandovski et al., 2013; Haraszti et al., 2014b; Que et al., 2015). Other variables related to CT are the gender (Randler et al., 2008; Roenneberg, 2012; Preckel et al., 2013; Piffer et al., 2014; Tonetti et al., 2016) and, to a lesser extent, the personality traits and psychopathological characters (Adan et al., 2010a; Loureiro & Marquez, 2015; Tonetti et al., 2016; Mirshamsi & Khoshsorour, 2019). Among all these interfering factors, age is the strongest (Jankowski, 2016). In eastern and western countries, it seems that there is a genetic basis in the CTs for both sex and age (Mishima et al., 2005; Hur, 2007; Melo et al., 2017; Pereira-Morales et al., 2018).

In young children, some studies did not find any effect of sex on CT (Simpkin et al., 2014; Doi et al., 2016; Zimmermann et al., 2016) and suggest a lack of any difference between the sexes (Wickersham, 2006; Nakade et al., 2012). Regardless of gender, several studies have found differences in ET and MT in young children and adolescents. Nakade et al. (2012) reported that 2-year old children had higher MT scores compared to 3 to 5-year old ones. According to Wada et al. (2009), infants in the Czech Republic and Japan show more ET. Wickersham (2006) reported that 2- and 3-year old children show extreme MT. The majority of the conducted studies reported that young children tend to show more MT (Roenneberg et al., 2007, Preckel et al., 2013; Arbabi et al., 2015; Qu et al., 2015; Carissimi et al., 2016) as well as the older people (like childhood) show more MT preference (Adan & Almirall, 1991; Adan et al., 2012; Di milia et al., 2013; Arbabi et al., 2015; Pereira-Morales et al., 2018), especially over the age of 60 years (Roenneberg et al., 2007). A recent meta-analysis, collecting 164 research that included 186,289 participants, concluded that men were on average more ET than women (Randler & Engelke, 2019) although the differences will diminish with age. Young women were more prone to MT compared to young men but with age, older women were less MT than older men. Another study showed that women had more tendency to MT than men; also, women went to bed earlier with more sleep time on the weekends than men (Mathew et al., 2019). Duarte et al. (2014) revealed an association between male sex and ET in adults.

Adolescence (12-17 years old) is a critical stage in which alteration in CT occurs from MT to a more pronounced tendency to ET (Dockray & Steptoe, 2011; Adan et al., 2012; Arbabi et al., 2015; Escribano & Díaz-Morales, 2016) and an increasing trend occurs in ET until nearly the age of 18-20 years (Hasler et al., 2015). Randler et al. (2017) stated that the peak of ET is at around the age of 16 years in girls and 17 years in boys, but after this peak, neither of the sexes shows differences in age groups. In another study, the maximum level of ET in women and men was reported at ages of 19.5 and 21 years, respectively (Roenneberg et al., 2007). Consequently, these results show that proclivity to ET in adolescence is an outcome of puberty (Robillard et al., 2014), social demands (school burdens), social associations, and family needs (Escribano & Díaz-Morales, 2013; 2016), and propensity has been observed in dissimilar cultures (Tonetti et al., 2015).

Antypa et al. (2016) noticed that being younger, male, having higher education, and having no partner or children are concomitant of ET. Similar results were obtained concerning that males

have more ET than females (Adan & Natale, 2002; Randler, 2007; 2008; Haraszti et al., 2014b; Ponzi et al., 2014; Fares et al., 2015; Tonetti et al., 2016; Fischer et al., 2017). Also, ET men have more sexual partners than women (Selvi et al., 2011; Adan et al., 2012; Maestripieri, 2014; Ponzi et al., 2014). In terms of CT, ET has an unbalanced sleeping shape (Bahk et al., 2014), which happens with a higher incidence of unstable menstrual cycles and more premenstrual, mental, and physical symptoms in women (Prat & Adan, 2013). Being in bed for a shorter period of time, in interaction with lower sleep quality, leads to aggressive behavior and internalizing behavioral problems in males (Meijer et al., 2010). Meanwhile, in women, shorter time in bed is related to a quicker increase in anxious and depressive behavior (McGlinchey & Harvey, 2015). So far, many studies have shown that daily sleepiness and poor sleep quality are more common in women than in men (Hara et al., 2004; Young, 2004; Hillman & Lack, 2013). Recently, a study conducted on 467 healthy young adults showed that anxiety symptoms were affected by daytime sleepiness and sex (Pereira-Morales et al., 2018), having a higher impact on women. Also, CT had a significant effect on all sample individuals, especially in MTs and there was a significant relationship between gender and anxiety symptoms in MTs. In terms of marital status Antúnes et al. (2015) reported a high rate of workers in the MT persons. Singles were reported more ET while in couples they showed more MT. In terms of relationship, Maestripieri (2014) found that both females and males with ET were more prone to be single than in long-term relations.

Behavioral problems and cognitive deficits are the consequences of sleep loss in children. This results not only in sleep quantity but also in sleep quality such as sleep efficiency (the entire time spent sleep), sleep latency (the amount of time between lounging in bed and beginning of sleep), and the regularity of the sleep-wake-cycle (Warren et al., 2017). In this regard, the results indicate that SPs in children as young as 4 years old anticipate later behavioral and emotional problems in adolescence (McGlinchey & Harvey, 2015), especially for depression (Bootzin & Stevens, 2005). A recent longitudinal study by Jiskrova et al. (2019), in a European sample of pregnancy and childhood, indicated that greater ET at age of 7 years significantly predicted greater sleep problems, lower sleep quantity on weekdays, and higher sleep quantity on weekends at age 11 years. Both ET children and adolescents slept fewer hours per night on weekdays. Moreover, SPs at the age of 16 years predict SP in adulthood (Díaz-Morales & Escribano, 2015) and older age has been correlated with lower sleep efficiency (Robillard et al., 2014; Bei et al., 2015). In sum,

this impaired sleep might have long-term effects on behavior, with its remaining results can be observed even years after regularization of sleep (Van der Heijden et al., 2013).

In some studies, the association between CT and personality traits has been stated (Qu et al., 2015: Randler, 2017). According to the Zukerman-Kuhlman Personality questionnaire (ZKPQ) in activity levels, lower scores were reported in ETs (Muro et al., 2009; 2011; Haraszti et al., 2014b). Also, a considerable number of studies have shown that ETs are more predisposed to impulsivity and novelty seeking or risk-taking traits (Adan et al., 2010b; Hasler et al., 2015; Berdynaj et al., 2016) and also higher neuroticism (Tonetti et al., 2009; Mirshamsi & Khoshsorour, 2019). Moreover, according to the NEO personality dimensions, more agreeableness, and consciousness (De Young et al., 2007; Randler, 2008, 2017; Tsaousis, 2010; Walker et al., 2014; Mirshamsi & Khoshsorour 2019), higher extraversion (Jackson & Gerard, 1996; Adan et al. 2010b, Randler et al., 2017; Mirshamsi & Khoshsorour, 2019), were reported in ETs.

Among other characteristics, ETs have shown more narcissism (Maestripieri, 2014), the propensity to discover the unknown (Randler, 2008; Kim et al., 2010; Antúnez et al., 2014; Piffer et al., 2014; Berdynaj et al., 2016), a higher rate of pessimism (Lester, 2015), and higher flexibility (Müller et al., 2015). In comparison, MTs reported more self-directedness and persistence (Adan et al., 2010a), more self-transcendence (Antúnez et al., 2014), a maximum level of resilience (Lee et al., 2016), and more coping strategies. In the performance aspect, MTs reported more concentration, alertness, problem-solving, more energy, and memory, and a higher motivation to exercise and self-esteem (Oliveira et al., 2020). In social interactions and attitude toward the future, MTs showed more satisfaction in life (Randler, 2008), psychological well-being (Antúnez et al., 2015), more mindfulness (Carciofo et al., 2014), higher enthusiasm to learn, the feelings about achievement (Roeser et al., 2013), planning more efficiency/accurately (Mohseni, 2019), and better reception toward social ethics (Antúnez et al., 2014). Altogether, as mentioned, different populations and cultures (Borisenkov et al., 2015), personality factors (Randler et al., 2017), age (Adan et al, 2012), and sleep (Randler, 2008) have a general impact on sleep-wake-cycle and CTs. Therefore, recent data suggest that changes in lifestyle, which leads to improving the functioning of CT in each country or society, would help reduce the risk of future mental health (Pilz et al., 2018).

1.3.2. Disruptions in circadian rhythms, circadian typology, and sleep on lifestyle

CR's ability to adapt to the environment is extremely useful for the survival of many species and is important for the regulation of sleep timetables, mood, stress quantity, and capacity to adapt at changes in time zones. CR and healthy behaviors in association with sleep (sleep hygiene) may lead to better physical health profit (Duggan et al., 2014; Vetter et al., 2015; Carvalho et al., 2018). However, the role of CR disruptions in risk to develop physical and mental disorders has remained uncharted (Wong et al., 2015), a recent study reported that misalignment in CR is strongly linked with higher problems in mental health (Pilz et al., 2018). Therefore, sleep hygiene is significantly related to sleep quality (Lebourgeois et al., 2004; Jefferson et al., 2005) and CTs are related to the sleep hygiene (Brown et al., 2002).

Troubles in CR are considered symptoms of many illnesses and are related to plentiful declines in the quality of life (QOL) (Lund et al., 2010; Wilson et al., 2019). In adult and aging people, CR disturbance is correlated with sleep impairment and damaged immune system function (Hickie et al., 2013; Jagannath et al., 2013). Problems in CR and SPs are also very usual in those with recognized severe mental illness including psychosis and depressive/bipolar disorders (Sheaves et al., 2016). Moreover, SP comorbidity with depression can be associated with drug misuse during adolescence (Alvaro et al., 2014). Therefore, the vicious cycle between SPs and mental disorders (Miller et al., 2015; Robillard et al., 2015) and CTs, which are risk factors for medical disorders (Papantoniou, et al., 2015), has made the circadian system the subject of treating several diseases including obesity, increased inflammation, or diabetes (Hickie et al., 2013; McClung, 2013, Bron et al., 2016). Among mental disorders, sleep-wake disorders, anxiety, bipolar/depressive disorders, and addiction have the strongest association with CRs (Liu & Chung, 2015). A survey study on 2,400 German students showed that physical disorders such as tension headaches, irritable bowel syndrome (IBS), and chronic back pain were positively associated with poor sleep quality, difficulty in falling asleep, daytime dysfunction, and use of sleep medication. Interestingly, these associations were significantly higher in participants who reported more levels of depression symptoms (Schlarb et al., 2017).

The National Institutes of Health (NIH, 1997) has described SPs related to complications in concentrating, reduced initiative, memory and cognitive problems, slower motor response, and

more mistakes of working memory in both adults and adolescents (Haraszti et al., 2014b). SPs have also been associated with lower general health, energy levels, and well-being (Duggan et al., 2014). Not surprisingly, sleepy adolescents may have more troubles dealing with stressful circumstances and lower endurance to frustration (Short, 2013b). It has been evidenced that brain regions presenting the greatest sensitivity to insufficient sleep are in prefrontal and inter-related limbic (McGlinchey & Harvey, 2015). Also, it has been suggested that the role of the frontal lobe is associated with sleep deprivation and decreased functioning (Pasula et al., 2018).

Many patients refer to psychiatric clinics with a range of sleep complaints, insomnia, extreme daytime sleepiness, and early awakenings that impair the important parts of their functioning and QOL (Barion, 2011; Wilson et al., 2019). Insomnia often begins with a specific difficulty including environmental stressors (e.g. losing a job) or through something that changes the sleep pattern (e.g. the birth of a baby or shift time of work). In some people, this process continues chronically. It is noteworthy that the role of factors including sleep anxiety, maladaptive sleep habits, and vulnerability has not yet been fully understood in sleep regulation mechanisms (Wilson et al., 2019). Adequate sleep patterns and sleep quality have a significant effect on cognitive and emotional functioning. Consequently, regularization of sleep-wake disruptions and its association with lower frequencies of future illness onset is a good suggestion (Robillard et al., 2015). Given the importance of the issue and for more accurately assess the quality of sleep, the Pittsburgh sleep quality index (PSQI) developed by Buysse et al. (1989) is a useful self-assessed questionnaire with good reliability (Cronbach's alpha of 0.83). The PSQI consists of 19 items that evaluate 7 dimensions or subscales of sleep over the past month including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, SPs, daytime dysfunction, and use of sleep medications with the creation of global sleep quality score.

SPs and CTs have been related to increased risk activities in several studies (Lee et al., 2012; Mak et al., 2010; Shochat et al., 2014), as well as high-risk sexual and more aggressive behavior (Haynes et al., 2006; Telzer et al., 2013). SPs like insomnia may increase the risk of suicide in several ways. First, insomnia is associated with the onset of mental illness (Pigeon et al., 2017), especially depression (Baglioni et al., 2011). Second, the effect that SPs have on a person's condition and mood reduces his/her ability to cope with environmental stressors, thereby leading to his/her poor response to stress and increased negative events of interpersonal life. Third, the

feeling of helplessness and a sense of lack of control can be the result of the negative effects of insomnia (Pigeon & Perlis, 2007).

Goldstein et al. (2008) studying 270 American students reported that those who had SPs showed more suicide attempts. In a study on a non-clinical sample of adolescents (12-13 years old) during a 1-year period, it was found that ET individuals were significantly associated with an increased risk for suicidality and impulsivity (Selvi et al., 2011). In line with this result, Short et al. (2013b) reported the same results such that ET individuals displayed more suicidality. In a recent study by Bishop et al. (2020) on 30,051 people with suicide attempts and 30,051 without suicide attempts, they found that insomnia, nightmares, sleep breathing disorders were associated with suicide attempts. They indicated that sleep medicine visits are effective in reducing the risk of suicide attempts after accounting for age, gender, treatment, and comorbid sleep disorders. Typical SPs like insomnia and hypersomnia have an association with ET (Vernet & Arnulf, 2009; Chan et al., 2014). Consequently, an increase in sleep pressure and an optimum or non-optimal cycle of CR can change the performance (Escribano & Díaz-Morales, 2014).

In DSM-5 (2013), mood disorders have been categorized into two separate types of 1) BD and related disorders and 2) depressive disorders. Therefore, instead of mood disorders considered in DSM-IV-TR (Spitzer et al., 2002), we use the actual classification of bipolar/depressive disorders in the present work. In BD patients, especially those with fast mood oscillates, ET is more prevalent (Logan et al., 2014). Young people with BDs have shown longer sleep onset latency, increased nighttime awakenings, worse sleep quality, and extended time asleep (Robillard et al., 2015). Individuals with BDs have fewer constant circadian sleep-wake forms, lower amplitude, lower day-time activity, and more fragmented night-time sleep compared with unipolar depression or healthy controls (Baron & Reid, 2014). In a recent study on 236 BD patients with and without suicidal attempts, a suicidal attempt was associated with female gender, familiar history, mixed episode MT tendency, and more SPs like insomnia and earlier onset of daily activity (Benard et al., 2019). In patients with BD, the males with stronger ET presented worse positive symptoms, such as hostility, grandiosity, suspiciousness, unusual thoughts, and disorganization (Fares et al., 2015). Although the exact site of the brain dysfunction in MDD or BD is unidentified, the midbrain dopamine system, or brain reward circuitry, lateral habenula, retina, olfactory bulb, and hippocampus are possible places in the circadian system for mood alterations (McCarthy & Welsh,

2012). Park et al. (2015) observed that ET individuals have greater depressive, cyclothymic, irritable, and anxious temperaments while MTs were significantly correlated with hyperthymic temperament. In another study, lower emotional intelligence and more prone to psychopathy were reported (Maestripieri, 2014). People with ET may die younger (Merikanto et al., 2014) and those who live longer may alter their CT with age to MT or IT (Maukonen et al., 2016) at the risk of suffering more metabolic harms (Ortiz-Tudela et al., 2010; Merikanto et al., 2015; Yong et al., 2016), coronary heart disease, and cardiovascular incidents (Baron & Reid, 2014; Boergers et al., 2014; Haraszti et al., 2014b; Kooij & Bijlenga, 2013; Hasler et al., 2015). This generally is accompanied by an increase in all causes of death (Yong et al., 2016). Recently, Carvalho et al. (2018), using Munich Chronotype Questionnaire (MCTQ) among 987 individuals, determined that ETs have poorer psychological well-being. Additionally, a study described that ETs presented greater levels of chronic fatigue in work, displayed less routine social rhythms, and was exposed to lower levels of light during their waking hours in comparison with MT and IT (Martin et al., 2012).

Men are likely to illustrate shorter nocturnal sleep, a greater delay in sleep-wake schedule, and a higher prevalence of delayed sleep-wake- phase disorder (Morita et al., 2015). After a year of follow-up in adults, it was found that older adults (≥ 60) have a greater decrease in wake time compared to youngers (≤ 44) (Bei et al., 2015). However, there is limited information about what is effective in changing the CT in puberty (Haradan et al., 2017). In teenagers, both biological and psychosocial factors encourage late bedtimes. In this regard, in 40% of adolescents biological effects at the beginning of puberty activate a change toward an ET orientation (McGlinchey & Harvey, 2015).

According to the National Sleep Foundation (2015) suggests, adolescents need to sleep between 8 and 10 hours, but only 15% reach 8.5 hours of sleep on weekdays (Hirshkowitz et al., 2015). Decreased self-esteem, low academic functioning, and poorer mental health at this age group have been related to inappropriate sleep (Roberts, & Duong, 2009). During adolescence, a dramatic progressive increase is observed in sleep shortage. The best functioning at school is longer than 600 min/night (Díaz-Morales & Escribano, 2015). There has been a general trend toward ET in the last decades in the population level (Müller et al., 2015) such that it approximately 40% among teens (Asarnow et al., 2014). During adolescence, struggles in the family and more autonomy

needs in the family environment are better predictors of a shift toward ET (Müller et al., 2015). Meta-analytic reviews described an association between shorter sleep duration and poor school/academic performance (Short et al., 2013a; Fares et al., 2015), worse working and lower intelligence (Díaz-Morales & Escribano, 2015) while more sleep is constantly correlated with better grades at school (Asarnow et al., 2014). Asarnow et al. (2014) found that late bedtimes at school were correlated with shorter total sleep time; however, short total sleep time was not related to emotional and academic performance. During free days, a postponement was visible both in sleep onset and wake time, which was in line with students' CR. It has been found that as the effect of CT was stronger than sleep duration in students (Önder et al., 2014), ET students reported more psychological distress (Prat & Adan, 2013), depression, insomnia, Attention Deficit Hyperactivity Disorder (ADHD), SUD (Antúnez et al., 2014), anxiety symptoms (Chan et al., 2014; Simor et al., 2015), and bulimia (Ghaseminejad et al., 2015).

Concerning the performance, higher concentration slips, slower reaction times, and impaired working memory (Carciofo et al., 2014) were observed in ET. The differences between working memory have been observed even in children in days of the week and times of the day. MT children showed their best memory performance at 8 am every day of the week but for ET children, the best performance was relatively close to the first days of the week and all hours of the day (Nasiri et al., 2019). MTs show somehow better academic performance (Randler, 2008; Haraszti et al., 2014a) and receive higher grade point averages (Önder et al., 2014) compared to ETs. Poor school performance is predicted by late bedtime (McGlinchey & Harvey, 2015). Therefore, ETs have more problems with the school in terms of absenteeism and a worse school functioning and achievement (Vollmer et al., 2013; Borisenkov et al., 2015; Zerbini et al., 2017). In this regard, since school starts in the early morning, MTs get better grades relative to ETs (Rahafar et al., 2016) because, after awakening, MTs have a higher activation level that may allow them better managing the school days (Schaal et al., 2010; Vollmer et al., 2013).

In comparison, ETs have later sleep-wake lifestyles. As schools mostly start in the morning hours of the day, those with later CT experience more sleep problems. Accordingly, a reduction in sleep length leads to lower mood and lower cognitive functioning (Preckel et al., 2013; Rahafar et al., 2016). In other words, sleep onset in ET children is generally about 1 h later than in MTs while differences in wake-up time are the same on the schedule of schools. Data show that early start

times at schools are related to many detrimental educational and health results but delayed school start times may have better consequences on performance (Boergers et al., 2014; Fischer et al., 2017). This difference between the cognitive function of MT-ET children could be a consequence of having poor eating habits. ET children reported more lack of vitamins, zinc, vitamin D, and riboflavin (Sato-Mito et al., 2011) because of avoiding late attendance in the school and leaving the house without eating breakfast. This process can lower performance and cognitive functions (Randler & Frech, 2009; Schmidt & Randler, 2010). In this regard, individuals with ET revealed more problems in eating behaviors that may negatively influence their weight (increased fast food and soda consumption) compared with MTs and ITs (Roenneberg, 2012; Konttinen et al., 2014).

A study by Martin et al. (2015) on 39 patrol police officers displayed that ETs have lower sleep efficiency and longer snooze time, spend more time awake after sleep onset, fall asleep later, have shorter and more frequent sleep bouts, alter sleep schedules during days off, and have shorter total sleep period than ITs (no subject-categorized as MT type in this research). Moreover, the ETs participants were more active during the first hours of their night shift. Hajaghazadeh et al. (2019) carried out a study on 120 nurses in university hospital-Iran with/without shift work. Up to 60% of nurses were IT, 24.2% were MT, and 15.8% were ET. A study carried out on 205 rotating shift workers and day shift workers in Iran revealed that most of the participants were IT (near 76%). Up to 80% of rotating-shift workers reported anxiety, while this rate in day-shift workers was up to 52.7%. Sleepiness status was reported more in rotating-shift workers than day shifts. Also, sleepiness, stress, and workload were diagnosed as fatigue factors. A Japanese study on 1170 adults aged 20-59 years demonstrated that ET is related to delayed sleep onset, a shorter period of sleep, and worsening in perceived quality of sleep (Kitamura et al., 2010). In Iran, Mozafari et al. (2016) conducted a cross-sectional study on 400 students and reported that 38.5% were ET, 34.3% IT, and 27.3% MT. MTs had more SPs and also worse sleep quality than ITs and ETs. Moreover, Isa-zadegan et al. (2013) researched 200 Iranian university students and showed that MTs were happier and more satisfied with their lives compared to ITs and ETs. However, the differences in CTs between the sexes were not described in these studies.

In a study on 3,699 students, Repa (2019) showed that about 70% of participants were SPs according to quality of sleep. These results showed a higher amount of SP among young adults compared to previous studies. In this line, participants reported more prevalence of insomnia than

the general population (over 55%). ETs showed more depression and anxiety symptoms than ITs and MTs. With increasing their ages, participants revealed more distress. MTs reported more social support than ITs and ETs. An interesting study was carried out on 940 Colombian adults (students and workers) who responded to a questionnaire about their family CT. This study is the first investigation to consider and report the mismatching between perceived family and individual CTs, sleep-wake patterns on weekdays and free days, diurnal subjective somnolence, and substance use. They found a mismatch between family and individual CT, especially for MT persons. Individuals whose CT did not match with their family were more prone to MT and individuals who matched with their family CT indicated higher levels of somnolence. Perceived MT families reported a higher average of diurnal subjective somnolence. In this study, women showed a higher average level of diurnal subjective somnolence than men. Participants with perceived ET family were more caffeine and alcohol users. Overall, subjects reported more IT and perceived family CTs were more ET. Persons who reported their family as MT introduced fewer hours of nocturnal sleep during free days. Perceived family CT was reported as an important factor in individuals' CT variance (Pereira- Morales et al., 2019).

1.3.3. Social Jet-Lag

SJL is an asynchrony among the biological clock of a person and the timing of social requirements such as faculty, school, or labor (De Souza & Hidalgo, 2014; Tavernier & Willoughby, 2014; Wong et al., 2015). On the other hand, SJL is a gap between internal circadian timing and typically early academic and/or work agendas (Hasler et al., 2013; Konttinen et al., 2014; Miller et al., 2015) or discrepancy between the weekend and weekday sleep timing (Roenneberg, 2012; Haraszti et al., 2014a). SJL can be a transient (Carissini et al., 2016) or a perpetual phenomenon (Díaz-Morales & Escribano, 2015). This phenomenon may account for why a greater ET has been associated with more negative psychosocial regulation. SJL happens around the age of 15-20 years (Haraszti et al., 2014a). Although pathways of SJL are still rather unknown, it has been determined that CD and disruption in CT lead to deregulation of one of the main stress response endogenous pathways called the Hypothalamic-pituitary-adrenal axis (Agorastos & Linthorst, 2016). In urban people, light spectra during the dark cycle, as well as manipulation of wake-up hours using an alarm clock, lead to an "artificial" awakening phenomenon, leading to more misalignment between the person and social demands (Carvalho et al., 2018).

Many adolescents endure SPs and SJL (Haslet et al., 2015; Carissimi et al., 2016). In terms of sleep duration, ideal performance in adolescents has been anticipated at over 9 h per night and more shortages of performance have been discovered in adolescents who sleep less than 8 h per night (Taylor & Bramowech, 2009; Short et al., 2013a; b). In this regard, the National Foundation Sleep in America Poll (NFSAP) has pointed out that 75% of students in the 12th-grade experience less than 8 hours of sleep per night (Owens, 2014). In this case, school schedules, social activities, and after-school occupations often lead to undesirable sleep (Bootzin & Stevens, 2005; Carissini et al., 2016). Students sleepless on school days and report more oversleeping during the weekends (Díaz-Morales & Escribano, 2015). In other words, adolescents try to wake up early during the school week and, instead, sleep late on weekends and vacations (Bootzin & Stevens, 2005; Hasler et al., 2015).

SJL happens especially in ETs because our society has a general orientation toward morning activities. It has been pointed out when the timing of classes is matched with students' preference, they report better academic presentations (Tavernier & Willoughby, 2014). Early start times at schools and adolescents' propensity to later wake-up times lead to misalignment in children's CRs (Warren et al., 2017). In terms of the class schedule, it has been found that the times in which classes begin may account for SP. Thus, changes in school times can promote sleep schedules (Baum et al., 2014) and later school beginning times could diminish SJL in youths (Roeser et al., 2013; Bartel et al., 2015; Minges & Redeker, 2016). A significant proportion of studies revealed similar weekend sleep durations between countries; but, in weekday sleep durations, they were varied (Huang et al., 2010; Owens, 2014). Roenneberg et al. (2003) and Wittmann et al. (2006) suggest that this discrepancy among the biological and social clocks is obvious in individuals with different types of CT during the week relative to the weekend.

Yong et al. (2016) pointed out that high SJL and sleep duration significantly increase the risk of poor workability. Besides, De Souza & Hidalgo (2014) reported that longer SJL hours are associated with older age in students. In primary school pupils, less SJL with an earlier midpoint of sleep was related to MTs (Arbabi et al., 2015). The influences of CT on academic performance may be exacerbated by SJL (Haraszti et al., 2014a; Zerbini et al., 2017). Age and SJL have a long-term impact on CTs and their stability, although in healthy adults no significant relationship was

observed (Miller et al., 2015). In pathologic samples, ETs were found to be more vulnerable to SJL (Roeser et al., 2013; Carciofo et al., 2014; Konttinen et al., 2014; Bei et al., 2015; Miller et al., 2015; Simor et al., 2015; Wong et al., 2015). Also, SJL was considered as a risk factor for depressive symptoms and impulsivity (McGowan et al., 2016; Müller et al., 2016b). A recent study on 35 healthy participants in the National College of Ireland, it was reported that CT and SJL were independent of each other. MTs were able to plan more efficiently/accurately than the ETs, while MTs on average took longer time to plan compared to ETs and ITs (Mohseni, 2019). Sleep duration on school nights and SJL was similar between men and women. Total school time negatively and SJL positively were associated with depressive symptoms (Mathew et al., 2019). Recently, Feliciano et al. (2019) conducted the largest study to examine the association of CT and SJL with accurate measures of adiposity. This study included 804 adolescents in which that ET and SJL were associated with greater adiposity only in girls; however, there were no associations with the cardiometabolic risk score for girls and boys. ETs reported more SJL and later sleep onset and obese adolescents showed more SJL, shorter sleep duration, and more prone to ET. Table 1 presents a selection of reviewed studies of the relationship among CT groups in healthy participants between 2006 and 2020.

Table 1. The relations among circadian typology (CT) and individual characteristics in healthy participants or the general population. a revision of the works published from 2006 to 2020.

Authors	**Sample**	**Measures**	**Main Results**
Adan et al. (2006)	N = 510 (men:182) 22.80 ± 4.14 yrs.	rMEQ SBS	MTs and ETs showed the greatest and lowest percentage of correct sleep beliefs, respectively, while ITs were in an intermediate position.
Randler (2008)	N = 1231(men: 579) 15.76 ± 4.83 yrs.	CSM Short Big Five Inventory	MT showed significant positive associations with agreeableness, and MT, and conscientiousness. Neuroticism was associated with ETs but only in females. Weekend oversleep was significantly and negatively associated with conscientiousness.
Hamidovic & Wit (2009)	N = 14 18-45 yrs.	Brief Questionnaire of Smoking Urges, Stop task, Profile of Mood States	SPs increased smoking and may specifically increase the tendency to smoke to decrease sleepiness.
Adan et al. (2010b)	N = 850 (men: 396) 21.98 ± 2.86 yrs.	rMEQ, DII,	Functional and dysfunctional impulsivity were reported more in men. MTs reported lower impulsivity than ITs and ETs. MT can be considered

			as a protective factor against impulse control disorders.
Kim et al. (2010)	N =361 Men:140 N = 19-79 yrs.	MEQ CES-D	ET had an association with depressive symptoms. Increased age was correlated with MT. The irregular sleep-wake-cycle was reported to be more common in ET.
Levandovski et al. (2011)	N = 4051 (men:2711) 44.1 ± 13.4 yrs.	BDI MCTQ	In 31- to 40-year-olds, misalignment of circadian and social time was a risk factor for increasing depression.
Isa-zadegan et al. (2013)	N = 200 (men: 24)	MEQ Q-LES-QSF	MT students showed more happiness and satisfaction compared with ITs and ETs. ITs showed more life satisfaction than ETs.
Díaz-Morales & Escribano (2013)	N = 887 (men:421) 14.2 ± 1.48 yrs.	MESC	ETs described shorter sleep length and scored higher on inductive reasoning relative to MTs. MT decreased with age and boys reported a higher score on MT. With age, sleep length decreased. Boys reported more sleep length than girls. ETs presented shorter sleep length, higher inductive reasoning, and lower school achievement than MTs.
Van der Heijden et al. (2013)	N = 333 (men:150) 9.97 ± 1.50 yrs.	CCTQ CSHQ	Girls were more ET and their parents reported fewer externalizing problems for boys. Moreover, ET scores negatively correlated with feeling rested upon waking up during weekdays. Longer sleep duration was related to more errors on the working memory task. ET predicted behavioral problems, with sleep mediating this effect and performance (working memory and sustained attention).
Merikanto et al. (2013)	N = 6071 25 to 74 yrs.	MEQ Self-report questionnaire for depression	ETs reported one or two-depressive symptoms, loss of interest, and use of prescribed antidepressant medication with a higher resting heart rate. They were more prone to depression. ITs had a significantly lower weight than MTs and ETs. Higher resting heart rate and risks for health dangers were reported in ETs.
Prat & Adan (2013)	N = 517 (men:173) 21.4 ± 2.9 yrs.	CSM, GHQ-28, SSS-V	ET subjects had a larger proportion of psychiatric cases and sensation-seeking than MT and IT.
Preckel et al. (2013)	N = 272 (men: 141) 15.6 ± 0.74 yrs.	LOCI, self-report questionnaire	ET was an important negative predictor of overall grade point average. ET students experienced more drugs (alcohol and nicotine), higher work avoidance, less conscientious, and were less performance motivated.
Roeser et al. (2013)	N = 273(men:107) Age = 15.18 ± 0.76 yrs.	MEQ SELLMO SDSC	ET and IT adolescents are affected by SJL. Stronger learning motivation was found in MT. ET was not per se associated with a low orientation to learning goals, but daytime sleepiness mediated this association. Moreover, ET had the strongest association between sleepiness and refusal to work.

Short et al. (2013a)	N = 385 (men: 231) 15 ± 61.0 yrs.	MEQ CES-D PSQI	Self-reported sleep quality also had a significant direct effect on sleep duration, with the sleep of poorer quality being related to shorter sleep duration. Sleep quality also had a significant effect on daytime alertness and mood. CT had a significant effect on depressed mood and an indirect effect on academic functioning. Sleep duration did not show a direct effect on adolescent activities.
Vollmer et al. (2013)	N = 1977 (men:1012) 13.38 ± 1.57 yrs.	CSM Task of Attention	In the attention test, MT was a significant forecaster of better grading and performance in attention tasks with a slower and more considerate completion strategy and faster and low impulsive strategy. Moreover, ETs made more errors and fluctuations in the strategy for solving the task.
Antúnez et al. (2014)	N = 700 (men:324) 22.25 ± 3.17 yrs.	rMEQ SSS-V	MTs showed higher persistence and higher resistance to fatigue, frustration, and difficulties. ET subjects tended to be more extravagant, temperamental, experience-seeking, and impulsive, with a higher tendency to explore the unknown, and more vulnerability to develop symptomatology and mental disorders.
Carciofo et al. (2014)	N = 673 (men: 200) 18-50 yrs.	rMEQ DF PSQI ESS , PANAS	Daytime sleepiness was positively associated with daydreaming and poorer sleep quality. Also, it was negatively correlated with a measure of problem-solving daydreams. ET was related to poor sleep quality, more mind wandering, and more daydreaming. Total PSQI positively predicted the neuroticism.
Escribano & Díaz-Morales (2014)	N = 669 (men: 318) 14.26 ± 1.31 yrs.	MESC	Attention increased throughout the school day in both ETs and MTs. Moreover, ET boys reached higher attention than ET girls. No difference was found between CTs.
Friborg et al. (2014)	N = 162 (men: 38) 24.3 ± 5.4 yrs.	Bergen Insomnia Scale FQ HADS	Sleep timing, sleep efficiency, and CT were delayed during December and modulated by depression and fatigue. For people living in sub-arctic regions, depressive symptoms during the night times exacerbate phase-shifting problems. Low levels of depression in a healthy student sample were correlated with seasonality in sleep timing.
Haraszti et al. (2014a)	N = 753 (men: 241) 21.23 ± 3.12 yrs.	MCTQ	Students with later sleep times achieved worse results in the morning of the free days. Meanwhile, an inverse trend was observed for the afternoon test takers. Circadian misalignment had a significant negative effect on educational performance and SJL was negatively correlated with the lecture-term grades. The effect of CT on academic performance was impaired by SJL.

Inomata et al. (2014)	N = 102 (men: 55) 21.7 ± 3.0 yrs.	MEQ PSQI ESS , CES-D	ETs were correlated with greater daytime sleepiness, poorer sleep quality, and a depressive tendency. A propensity toward was linked with a later bedtime, wake time, and mid-time measured by actigraphy and was related to poorer sleep quality.
Jankowski (2014)	N = 386 (men: 119) 21.15 ± 4.23 yrs.	MEQ, UWIST, Formal Characteristics of Behavior – Temperament Inventory.	Lower and higher emotional negative mood and reactivity was related to ET being. ETs were vulnerable to developing negative symptoms of stress. Endurance was a protective factor against the negative consequences of social jet-lag.
Maestripieri et al. (2014)	N = 501 (men: 349) 28.72 ± 2.39 yrs.	rMEQ Self-report questionnaires	ET was associated with higher risk-taking in women. Both ET's men and women were more likely to be single than in long-term relationships. Men had significantly higher mean cortisol levels than women. Sleep patterns and sex were suggestive predictors of mean cortisol.
Matamura et al. (2014)	N =314 (men= 88) (data not shown)	GHQ	Relation among sleep habits and mental health status were statistically significant. Late bedtime and short sleep duration could forecast subsequent development of depression and anxiety, including suicidal or self-injury risk. Poor mental health in adolescents might be solved by an intervention in sleep habits.
Önder et al. (2014)	N = 1343 (men: 500) 21.01 ± 1.78 yrs.	PSQI MEQ Adjective Based Personality Test	SJL and conscientiousness were the chief predictors of academic achievement. Conscientious students were more motivated and more MT. Sleep quality did not associate with academic achievement. The accomplishment of female students was high and the academic Impetus of female MT was higher.
Piffer et al. (2014)	N = 201 (men: 110) 28.58 ± 2.01 yrs.	rMEQ Saliva test	ET pattern was more frequent in men, although the CT was not significantly related to the sleep amount. The main effect of CT was observed on the Graduate Management Admission Test scores. The association between CT and intelligence was in the high range of intellectual ability and academic achievement.
Ponzi et al. (2014)	N = 172 (men: 86) 28.8 ± 0.4 yrs.	rMEQ, Domain-Specific, Risk-Taking Scale Big Five Inventory	There was no significant relationship between ethnicity and CT. ET was linked with greater risk-taking across the five risk domains independently of the effects of sex, age, or personality.
Randler et al. (2014)	N = 291 (men: 65) 22.14 ± 2.95 yrs.	BIS, inventory Big Five inventory	In MTs, drive and fear were higher but fun-seeking was more in ETs. MTs students were more conscientious. BIS total score was related to a higher inhibition in MTs and they were more proactive and introverted than ETs.
Rique et al. (2014)	N = 222 (men: 143) 22.3 ± 3.8	MEQ, PSQI, ESS	More ET medical students had poor quality of sleep (61.5%). There was no significant relationship between CT and age or the season of birth.

Tavernier & Willoughby (2014)	N = 780 (men:224) 19.0 ± 0.90 yrs.	LCA Self-report questionnaires	Morning-good and evening-good subgroups stated significantly better intrapersonal adjustment. ET subgroups showed higher scores on weekend delay and alcohol consumption.
Vollmer et al. (2014)	N = 741 (men: 446) 12.89 ±1.05 yrs.	CSM BIG-5 Inventory	Computer game usage time and addiction were associated with sex and CT. ETs, youths (11-16 years), and male students had higher computer game addiction scores than MTs.
Antúnez et al. (2015)	N = 1922 (men: 978) 30.08 ± 10.53 yrs.	rMEQ	In MTs, there were more workers and couples. A higher proportion of singles was ETs. The results showed that ET could be a risk factor for the development of psychological problems and mental disorders. In comparison, the MT could be considered as a protective factor.
Díaz-Morales & Escribano (2015)	N = 796 (men:371) 14.1 ± 1.48 yrs.	MESC School Sleep Habits Survey	SJL was negatively associated with academic achievement, cognitive abilities, and general cognitive ability. Also, it may be more harmful to girls' performance. Girls reported a longer time in bed on weekends.
Jeong et al. (2015)	N = 302 (no male) 18–65 yrs.	CSM, MDQ BSDS	ET may be more related to mood fluctuation than MT. The CT distribution was 14.6% for MT, 76.3% for IT, and 9.6% for ET.
Kang et al. (2015)	N = 503 (men: 288) 22.55 ± 2.79 yrs.	SSS-V CSM	ETs were associated with high impulsivity. CT was associated with psychiatric problems interrelating with some aspects of personality traits such as inhibitory control.
Lester (2015)	N = 194 (men:54) 21.6 ± 1.4 yrs.	BDI, The Beck Hopelessness Scale, The Defeat Scale, MEQ	ETs had higher scores on measures of depression, hopelessness, defeat, and entrapment. But, in terms of suicidal attempts scale, there was no significant report based on past suicidal ideation or attempts.
Loureiro & Garcia-Marques (2015)	N = 134 (men:45) 20.99 ± 7.27 yrs.	rMEQ	The majority of participants were classified as IT (52.2%). In comparison, MT and ET include 30.6% and 17.2% of the participants, respectively. It shows that individuals are aware of their CT.
Martin et al. (2015)	N = 39 (men: 28) 28.9 ± 3.2 yrs.	MEQ	ET showed lower sleep efficiency and longer snooze time, spent more time awake after sleep onset, fall asleep later, had shorter and more frequent sleep bouts, altered sleep schedules during days off, and shorter total sleep period, were more active during the first hours of their night shift, and had poorer sleep quality than ITs (no subject was categorized as MT).
Merikanto et al. (2015)	N = 10503 (men:1316) 25-74 yrs.	MEQ	Women showed more ET tendencies than men. ETs were significantly more depressed than the ITs and the ITs were significantly more depressed than the MT.
Park et al. (2015)	N = 641 (men: 376) 22.7 ± 3.71 yrs.	CSM	MTs (18.1%), ITs (62.7%), and ETs (19.2%) ET were considerably correlated with greater depressive,

			cyclothymic, irritable, and anxious temperaments, while MTs were notably associated with hyperthymic temperament.
Qu et al. (2015)	N = 295 (men: 148) 37.34 ± 9.39 yrs.	rMEQ	More risky driving, aggressive driving, negative cognitive/emotional driving, drunk driving, self-reported traffic accidents, penalty points, and fines were associated with ET.
Simor et al. (2015)	N = 756 (men;189) 25.3 ± 5.8 yrs.	MEQ-14, AIS , ESS ,BDI , PSS , GHQ	ET is an independent risk feature for higher negative emotionality associated with circadian misalignment scores. No significant effect was obtained concerning the interplay between CT and sleep problems.
Sheaves et al. (2015)	N = 1403 (men: 612) (not specified)	MCTQ Sleep Condition Indicator MDQ DASS-21 SCL	Higher levels of insomnia (71.7%) in the high-risk group also showed more ET. There was a strong association between insomnia and both depression and anxiety and weak associations were found between CT and both depression and hypomania. High-risk groups had poorer sleep compared to those individuals with just one subsyndromal symptom.
Tonetti et al. (2015)	N = 36 (men:24) 18.14 ± 0.49 yrs.	MEQ-CA MSQ	ET was related to a delayed phase of the sleep-wake-cycle. Better sleep quality was associated with better school achievement. A substantial positive association was observed between sleep efficiency and exam grades.
Antypa et al. (2016)	N = 1944 (men: 663) 42.8 ± 12.7 yrs. (depressed/anxious: 676 remitted: 831; healthy control: 437)	MCTQ IDS	A clear association was reported between MDD and ET. Current depressive and/or anxiety disorders were associated with an ET. MDD was associated with ET. MT reported a worse mood in the morning.
Berdynaj et al. (2016)	N = 86 (men:19) 18-43 yrs.	MEQ, PSQI, STAI EPQ-R	There was no significant effect between CT and sequential risk. A clear relationship was found between ET and increased negative processing and between reduced latency to correctly recognized personality traits and more risk-taking.
Jankowski (2016)	N = 974 (men: 321) 21.7 ± 2.0 yrs.	CES-D CSM	MT was related to less depressive symptoms in depressed/somatic and positive effects and unrelated to interpersonal associations. The results specify the importance of the morning effect, suggesting the affluence of transition from sleep to an awake state, sleep inertia, disruption of the circadian regulation of positive affect characteristic for depression.
Merikanto et al. (2016)	N = 469 (men:146) 18–29 yrs.	SCID-I	ETs reported higher dependency on alarm clocks, poorer health status and quality of life (QOL), more sleeping problems, daily tiredness, and seasonal variation in mood and behavior. ETs and ITs had more problems in feeling refreshed after waking up. Preference toward ET was more frequent in three or more mental disorders, more burnout, and more usage of drugs.

Mozafari et al., (2016)	N = 400 (men: 164) 23.13 ± 3.11	MEQ, PSQI, BMI, ISI	Of 400 students, 109 were MT, with the IT and ET being the next majorities. The majority of ET and MTs students had poorer sleep quality.
Paine & Gander (2016)	N = 28 (not specified) 41.1 ± 4.7 yrs.	MEQ	MT had significantly earlier sleep timing. On weekdays, ET had later sleep start times.
Tonetti et al. (2016)	N = 379 (men: 147) 31.2 ± 10.9 yrs.	rMEQ ZKPQ	ETs were more impulsive and more sensation seekers. Also, they had more delayed sleep-wake phase cycles and lower activity factors than MTs.
Yong et al. (2016)	N = 2474 (men: 1829) 41.81 ± 10.19 yrs.	MCQ	Sleep duration was positively related to better self-perceived health and workability. High SJL and shorter sleep duration were correlated with decreasing workability.
Randler et al., (2017)	N = 26,214 (men: 12,531) 14.68 ± 6.04 yrs.	CSM	Sex differences arise during puberty and remain until 30 years Turn toward MT is 15.7 years in girls and 17.2 boys. At the age of 0-1 year, 70% were MT, and about 1% ET. Meanwhile, at the age of 16 years, only 5% were MT and 19% were ET.
Togo et al. (2017)	N = 3032 (men: 105) 20-59 yrs.	MEQ CES-D	More ET and shorter sleep duration on the day shift were independently related to higher levels of depression, which may explain the relations between rotating shift workers and depression. Sleep duration on day shifts was significantly shorter in rotating shift workers.
Carvalho et al. (2018)	N = 987(men: 327) 43.93 ±12.51 yrs.	MCTQ, GSE, WHO-5	Work end time affected the relationship between sleep onset time and psychological well-being. There was an association between psychological well-being and sex, sleep onset, and self-efficacy. There was a link between work end time in the interaction with sleep onset time.
Putilov (2018)	N = 2393 (men: 1021) Age not specified	CES_D, SAS, SCL, SWPAQ	Depressive symptoms were found to be associated with MT rather than ET. The association was weaker but remained significant even after accounting gender, age, physical health, and flexibility of their sleep-wake-cycle. Those with higher depression symptoms reported higher seasonal changes in mood, behavior, and well-being.
Feliciano et al. (2019)	N = 804 (men: 386) 13.2 ± 0.9 yrs.	Actigraphy, MES-C	No associations were found with the cardiometabolic risk score for either sex. ET and SJL were associated with greater adiposity in girls but not in boys. ETs reported more SJL and later sleep onset. Obese adolescents showed more SJL, shorter sleep duration, and more prone to ET.
Hosseini et al. (2019)	N = 205 (men: 127) 32.27 ± 6.17 yrs.	CIS, MEQ, ESS,	Almost all of the participants were reported as IT. Most of the rotating-shift workers were male. Up to 80% of rotating-shift workers and 52.7% of day shift workers reported anxiety. More sleepiness status was reported in rotating-shift than day shift workers.

			Factors of fatigue were diagnosed as sleepiness and stress workload.
Mathew et al. (2019)	N = 3058 15.59 ± 0.77 yrs.	CES-D, BMI,	Sleep duration on school nights, SJL, and depressive symptoms were similar between men and women. Women showed more tendency to MT than men. In women, total school time negatively and SJL positively were associated with depression. Women were more depressed than men. Going to bed earlier and more sleep on the weekends was more in women.
Mirshamsi & Khoshsorour (2019)	N = 100 Age not specified Sex not specified	MEQ, NEO-FFI	MTs had higher consciousnesses and agreeableness while ETs were more neuroticism, extroversion, and openness to experience.
Nasiri et al. (2019)	N = 100 Sex not specified 5-6 yrs.	CMEP, CCTQ, Kim Karad visual memory test	MT children showed their best memory performance at 8 am every day of the week but for ET children the best performance was relatively close to the first days of the week and all hours of the day.
Repa (2019)	N = 3699 (men:882) 22.21 ± 3.73 yrs.	PSQI, K10, ISI, ESS, HADS,	Around 70% of participants revealed SPs according to quality of sleep. These results showed a higher amount of SP among young adults than before. ETs showed more depression and anxiety symptoms than ITs and MTs. With age, participants reported more distress. MTs reported more social support than ITs and ETs and more prevalence of insomnia (over 55%) than the general population.
Pereira-Morales et al. (2019)	N = 942 (men: 465) 21.8 ± 5.0 yrs. N = 786 students 20.8 ± 2.9 yrs. N = 156 workers N = 27.9 ± 8.6 yrs.	CSM, HNS, ESS	Women showed a higher average level in diurnal subjective somnolence than men. Perceived MT families reported a higher average of diurnal subjective somnolence. Subjects reported more IT and family CTs were more ET. Individuals who reported their family as MT reported fewer hours of nocturnal sleep during weekends. Perceived CT family was an important factor in individuals' CT variance. Individuals whose CT did not match with their perceived family were prone to MT. Also, individuals who matched with their family CT showed higher levels of somnolence. Besides, participants with ET family showed more often caffeine and alcohol use.
Randler and Engelke (2019)	N = 186,289 (men: 75.622)	MEQ, rMEQ, CSM	Men showed more ET than women. At a young age, women were more MT than men, but with age, older women were less MT in comparison to older men.
Bishop et al. (2020)	N = 60.102 (men: 52,337) 48.6 ± 15.4 yrs.	Recorded data ICD	SPs reported a large number of insomnias, sleep breath disorder, and nightmares. Insomnia and sleep breathing disorders are positively related to suicide attempts. Taking sleep medicine was considered a reducer of risk of suicide attempts.
Druiven et al. (2020)	N = 1,417 (men: 308) 18-65 yrs.	MCTQ, CIDI, BAI	Over a 7-years follow-up, CT was found to be stable. CT scores were negatively related to the severity of depression, but not anxiety. Change in CT and the

			severity of depressive symptoms may be explained by alteration in sleep patterns or sleep duration.
Oliveira et al. (2020)	N = 401 18-60 yrs.	rMEQ, MRhI	Irritability, anxiety, sadness, and talking to friends were more in women. Men reported more problem-solving, sexual arousal, and motivation to exercise. MTs showed more concentration, alertness, problem-solving, energy, memory, motivation to exercise, and self-esteem. ETs reported all of these features later in the day.

AIS (Athens Insomnia Scale); ; BAI (Beck Anxiety Inventory); BDI (The Beck Depression Inventory); BDI-9 (Short Beck Depression Inventory); BIS (Bergen Insomnia Scale); BSDS (Bipolar Spectrum Diagnostic Scale); BMI (Body Mass Index); CCTQ (Children's Chronotype Questionnaire)- CES-D (Center for Epidemiological Studies for Depression Scale); GHQ (General Health Questionnaire); CIDI (Composite International Diagnostic Interview); CIS (Checklist individual strength); CMEP (Children Morningness-Eveningness Preference); CSHQ (Children's Sleep Habits Questionnaire); CSM (Composite Scale of Morningness)- DASS-21 (Depression Anxiety and Stress Scale); DF (Daydream Frequency); DII (Dickman's Impulsivity Inventory); EPQ-R (Eysenck Personality Questionnaire Revised); ESS (Epworth Sleepiness Scale); FQ (Fatigue Questionnaire); GSE (General Self-Efficacy Scale); HADS (Hospital Anxiety and Depression Scale); HNS (Hours of Nocturnal Sleep); ISI (The Insomnia Severity Index); K10 (Kessler Psychological Distress Scale); LOCI (Lark-Owl Chronotype Indicator); MCTQ (the Munich Chronotype Questionnaire); MDQ (Mood Disorder Questionnaire); MESC (Morningness–Eveningness Scale for Children); MEQ (Morningness–Eveningness Questionnaire); MEQ-CA (Morningness–Eveningness Questionnaire for Children and Adolescents); MRhI (Mood Rhythm Instrument); NEO-FFI (Neo Five Factory Inventory); PANAS (Positive and Negative Affect Schedule); PSQI (Pittsburgh Sleep Quality Index); PSS4 (Perceived Stress Scale); Q-LES-QSF (Quality of Life and Enjoyment and Satisfaction Questionnaire); rMEQ (Reduced Morningness-Eveningness Questionnaire); SAS (Zung Self-Rating Anxiety Scale); SBS (Sleep Belief Scale); SCL (Symptom Checklist Inventory); SCID-I (Structured Clinical Interview for DSM- IV-TR); SELLMO (Scales for Determination of Learning and Achievement Motivation; SDSC (Somnolence of the Sleep Disturbance Scale for Children); SSS-V (Sensation Seeking Scale-V); SWPAQ (Sleep Wake Pattern Assessment Questionnaire); UWIST (university of Wales Institute of Science and Technology Mood Adjective Check List); STAI (Spielberger State/Trait anxiety inventory); WHO-5 (World Health Organization Five-item Well-being Index); ZKPQ (Zuckerman Kuhlman Personality Questionnaire).

1.4. Chronotherapeutic, nonpharmacological and common pharmacological treatments

CR and sleep studies have led to the description of nonpharmacological therapies of psychiatric disorders that can be implemented in everyday practice. These clinical interventions, called chronotherapeutic, are based on controlled exposures to environmental motivations that imply biological rhythms (Dallaspezia & Benedetti, 2011). Some of these treatments include bright light therapy (BLT) and sleep deprivation, defined as the controlled contact to environmental motivations. They can act on biological rhythms to reach therapeutic results in managing psychiatric circumstances (Benedetti & Colombo, 2011).

Almost all the successful treatments for bipolar/depressive disorders affect CRs. It seems that the changes, rearranging, and maintenance of these rhythms shaped by these treatments are vital for the therapeutic results (McClung, 2007). Also, other chronotherapeutic treatments such as enhancing healthy sleep, daily activity, and light therapy may provide useful support for rehabilitative procedures in people with psychotic disorders such as schizophrenia (SZ) (Bromundt et al., 2011; Dallaspezia & Benedetti, 2011). The use of chronotherapies, including the sleep-wake schedule (Foster et al., 2013) is very operational to organize CR and also useful in the treatment of MDD (Brooks & Canal, 2013; Chan et al., 2014). The strategy for creating the connection between bipolar/depressive disorders and CRs is mainly based upon several therapies found to be useful for decreasing the symptoms and enhancing the response to treatment.

Perhaps, the best-known remedy in this regard is light therapy for SAD (Bechtel, 2015). Light therapy as a noninvasive effective treatment for a whole spectrum of bipolar/depressive disorders is attractive for specialists because of its safety, fewer side effects, and easy use (McClung, 2007). In young people with a primary diagnosis of depression, BD or psychotic disorders have been discovered as similarly disturbed delayed and disorganized CTs. Therefore, therapeutic interventions planning to stabilize sleep-wake timetables at an earlier age-appropriate time may be pertinent to youth in several mental disorders (Robillard et al., 2015). In this regard, interventions to recover sleep quality per se influence all the associated disorders (Sheaves et al., 2016).

A combination of other therapeutic approaches such as Motivational Interviewing (MI), Cognitive Behavior Therapy (CBT), and family therapy can be operative for reducing substance use among SZ patients for at least one year. The 90-minute group therapy is effective against psychosis and substance use. Contingency Management (CM) is also effective against cannabis use and bipolar/depressive disorders (Kelly et al., 2013). CBT for insomnia (CBT-I), as an efficacious non-pharmacological treatment for insomnia which has had positive effects on sleep efficiency and depressive symptoms along with benefits on the better achievement of energy levels, self-esteem, and productivity (Voinescu et al., 2010; Bei et al., 2015). In this regard, a recent pilot study on CBT-I on 10 veterans showed a significant improvement of depression and insomnia and the shift of ET toward MT (Boland et al., 2019). Mindfulness-Based Stress Reduction (MBSR) is another suitable method as a treatment for stress-induced SP, attention control, chronic pain, depression, and anxiety (Kabat-Zinn, 1994; Bootzin & Stevens, 2005; Zhang et al., 2015). Taken together, the results suggest that timely regulation of sleep might act as a protective factor for behavioral problems in later development (Van der Heijden et al., 2013).

Some sleep medications containing antihistamine may cause sedation (Neubauer, 2009). Physicians do not recommend these medications as long-term treatments for SPs due to negative effects on the natural sleep-cycle and side effects such as morning grogginess, daytime sleepiness, and impaired alertness and judgment (Jones et al., 2003; Singh et al, 2015). Additionally, it has been evidenced that the long-term and efficient effects of these drugs are not considerable (Singh et al., 2015). Other medications used to treat SPs, especially in insomnia, are Ramelteon (as a reducer of the amount of time it takes to fall asleep) (Roth et al., 2006) and antidepressants like doxepin, amitriptyline, mirtazapine, nefazodone, nortriptyline (with sedative properties), and acamprosate. Another group of medications of SPs is benzodiazepines (alprazolam, diazepam, lorazepam, and triazolam) or benzodiazepine analog (zaleplon, zolpidem, and zopiclone), which are sedative and/or hypnotic medications. These drugs in long-term use can have side effects like withdrawal symptoms (e.g., anxiety, irritability, seizures, daytime sedation, cognitive impairment, motor incoordination, and rebound insomnia) (NIH, 2005).

Melatonin is a popular dietary supplement taken to promote sleep. This drug as a pharmacological treatment in the evening improves sleep-wake times of people with SPs. Melatonin plays an

important role in the circadian system and is a useful treatment for CR especially sleep-wake disorders (Hughes & Badia, 1997; Li et al., 2019). Abnormalities have been reported in melatonin secretion in some psychiatric disorders, especially in SAD (a condition of regularly occurring depressions in winter with remission in the following spring or summer) and MDD (Crasson et al., 2004). For example, depressed subjects showed more variation in salivary melatonin and more melatonin levels than the control group (Bouwmans et al., 2015). It seems that melatonin receptor 1 in SQN increases in MDDs (Wu et al., 2006). However, other studies have stated no differences in circadian melatonin levels in SAD and MDD patients (McClung, 2007).

Melatonin administration helps reduce time to fall asleep (Auld et al., 2017) and induce sleep in people with disrupted CR such as those suffering from chronic insomnia and blindness (Brzezinski et al., 2005). Scientific studies have found that melatonin also helps prevent sleep disturbances related to shift work and jet lag, especially in people who cross five or more time zones (Arendt & Skene, 2005). When used to recover sleep, melatonin should be taken approximately several minutes before bedtime. However, there has been no evidence about its harmfulness so far and even some data show that melatonin can treat chronic insomnia in some people (Lemoine et al., 2011). Findings highlight the importance of early intervention in SPs, as well as the beneficial effects of physical and mental health from an early age (Repa, 2019). In this regard, chronobiological treatments could also indirectly be helpful to decrease CR problems (Hühne et al., 2018) and data suggest that combining therapeutic approaches may be more effective than using one (Neubauer, 2009). Here although our goal is not to study different types of treatments, they all have benefits. However, due to the rhythmic differences of individuals, many traditional therapies maybe not very suitable for people recovering from disorders.

1.5. Substance Use Disorder

In DSM-5, the diagnosis of SUD is based on a pathological pattern of behaviors associated with the use of the substance and is categorized into 4 criteria. The first criterion is the impaired control of substance use, which comes from using the substance in larger amounts or over a longer period than was originally planned. Also, it may be due to a tendency to cut down or control substance use. It involves spending a great deal of time in obtaining or using the substance and recovering

from its effects or exhibiting an intense tendency toward the drug that may occur in an environment where the drug previously was obtained or used. The second criterion is social impairments, including failure in doing social and domestic responsibilities, continuing to use SUD despite the arisen problems, and reduced social activities because of substance use. The third one is risky behavior, which implies placing oneself in a dangerous situation, despite knowing the possible physical or psychological difficulties. As the last group of criteria, pharmacological criteria include tolerance (requiring a prominently increased dose of the substance to attain the anticipated effect) and withdrawal (a syndrome that occurs when blood concentration in the individual decreases after long and heavy use of the substance) (American Psychiatric Association (APA), 2013).

SUD as a highly frequent psychiatric disorder, costing around billions of euros to the states (European Monitoring Centre for Drugs and Drug Addiction, 2011), creates a major health issue characterized by cognitive, behavioral, and physiological indicators. SUD affects millions of adults and their families, with more than half a trillion dollars, and lead to more than 75,000 deaths in the United States each year (Conroy & Arnedt, 2014). Substance use and addiction to drugs also modify the pattern of neurotransmitter liberation (Wulff et al., 2010). Therefore, SUD changes the homeostatic balance of several neurotransmitters systems, such as acetylcholine, GABA, dopamine, glutamate, norepinephrine, and orexin, making them prone to more deterioration (Conroy & Arnedt, 2014; Matzeu et al., 2014; Baimel et al., 2015).

The use of both cigarettes and alcohol, despite their declined use in recent decades, impairs the sleep-wake-cycle and inadequate sleep (Warren et al., 2017). The use of these substances disrupts the sleep-wake-cycle (Bartel et al., 2015). These effects have a significant role in the prognostication of SUD (Warren et al., 2017). In general, addiction is a behavioral and biopsychosocial phenomenon and regularly is hard to detach the psychological from biological and social regularity (Szerman et al., 2013).

Following the decline in illegal drug use in the 1980s, its use was increased among teenagers in the early 1990s. In this regard, in high school students, marijuana is the most illicit drug while youth prefer marijuana and alcohol. Monitoring the Future (MTF) shows that despite the difference in substance use according to gender, these data show higher rates of illicit drug use by males. Moreover, other treatment studies have described that women use higher rates of illegal drugs than

males, including methamphetamine, cocaine, and heroin (Bootzin & Stevens, 2005). A systematic review by Hunt et al. (2020) reported that the prevalence of SUD in Asian countries was significantly lower than in the United States or other nations. Also, men were 2-3 times more prone to the risk of SUD than women. In the study by Roshanpajouh et al. (2020), continued substance use in men compared to women was 6,6 times more in the group of 15-29 years and 13,8 times more in the group of 45-64 years. Even higher mortality and SUD related problems were reported in men compared with women (Ghoreishi et al., 2017; Rostami et al., 2017; 2018, Rostami & Rezaeian, 2019). Alcohol SUD in female gender leads to an increase in testosterone levels, menstrual disturbances, and even infertility (Peck et al., 2011). In contrast, in the male gender, in addition to increasing the testosterone hormone, it may affect sperm quality (Jensen et al., 2014). A recent study in Iran reported that the rate of prior history of tobacco smoking in female and male students is up to 14% and 22%, respectively (Vakilian et al., 2019). Overall, most studies similarly conclude that men are more addicted to substance use than women, especially in Iran (Baumann et al., 2007; Lotfi et al., 2016). One of the reasons for the higher rate of SUD and mortality of men is that they have higher freedom of action and social relations compared with women in Iranian society. Therefore, men have higher access to drugs. In other words, women's relationships in Iranian society are more controlled by families, which makes them less likely to seek substances (Zarrabi et al., 2009).

Among factors that rise vulnerability to addiction are the positive family history of addiction (heritability and child-rearing practices) (Coviello et al., 2004; Kendler et al., 2008), early contact with drug use (adolescence period is a risk factor), the experience of high-risk environments (typically, socially stressful environments), psychological and sociocultural characteristics (Lee et al., 2004), and the presence of mental diseases (e.g. bipolar/depressive disorders, ADHD, psychosis, and anxiety disorders). The chronic use of the substance may result from a tendency to lighten negative effects such as anxiety or depressed mood, physical pain reliever, to recover sleep, or to increase the experience of pleasure (Conroy & Arnedt, 2014). Drug use is related to a mixture of elements including genetic factors, social features (male gender, young age, low income, education, peer group, parental behavior), psychological and personality factors such as low conscientiousness, low friendliness, high extraversion, and neuroticism (Teesson & Proudfoot, 2013; Randler, 2008; Ghaseminejad et al., 2015; Qu et al., 2015; Boogar et al., 2015). These factors appear as risk features that vary from one culture to another (Suttajit et al., 2012). For example, in

Iran Farjad (1995) divided the effective causes of substance use in 3 categories. These categories are individual factors such as pleasure, curiosity, psychological and individual problems, family factors such as the existence of consumers in the family, family problems, and social factors such as availability of substance and growth of the industry. In other research in Iran, Baghiani-moghadam et al. (2008) point out other factors such as addicted friends, or no assertiveness as the important causes for the tendency of young people and individuals to use the substance. Boogar et al. (2015) reported that personality traits and sociodemographic factors have a key role in the tendency toward SUD and related perceived outcomes.

Some social, cultural, religious, and economic differences exist between Iranian populations and other countries in the use of the substance. This requires further research and evaluations among the Iranian population to determine the prevalence and patterns of drug use (Zamani et al., 2019). There are many problems with the use of drugs among Iranian youth and adolescents (Momtazi et al., 2010). This trend is increasing at least once in a lifetime among adolescents approximately 30-32%, and 7% of high school students with smoking and illicit drug use (Allahverdipour et al., 2009). A study from Shiraz city of Iran reported that 32% of 10th-grade students had consumed alcoholic beverages and 2.1% have had drug-use experience (Ayatollahi et al., 2005). In Tabriz (Iran), the consumption of alcoholic beverages and other drugs in students was 12.7% and 2%, respectively (Mohammadpoorasl et al., 2007). In a recent study on 264 teenagers admitted to substance use treatment, 75 (28.5%) of them reported using some kinds of substance in the week before the admission. Also, 37% and 50% of individuals in the old and young teenage groups were diagnosed as SUD, with more opioid and sedative drug users in old teenagers. Also, young teenagers hid their substance use more than the older ones (Zamani et al., 2019).

In the United States, it is estimated that 8 to 10% of people who are 12 years of age or older (i.e. 20 to 22 million people) are addicted to drugs (Volkow et al., 2016). This rate has been reported by the Substance abuse and mental health services administration (SAMHSA) (2017). From the therapeutic aspect, every year around 2.2 million Americans take treatment for cocaine or cannabis abuse in clinics (Schierenbeck et al., 2008). A study in the United States indicated that Asian Americans had the lowest prevalence of SUDs compared with other societies (Compton et al., 2007), although little is known about SUDs among Asians. SUD, especially in Chinese, Indian, Korean, and Vietnamese populations was lower compared to other Asian countries (Lee et al.,

2004). In Korea, it was reported that alcohol use is the most common disorder among SUDs (Cho et al., 2007) around 12.2 million in the adults (men 18% and women 6.4%) (Hong et al., 2017). Except for cannabis, the prevalence of all types of substance use in the Middle East is higher than worldwide estimations (World Health Organization (WHO), 2017).

The Anti-Narcotics law of Iran, as amended on the 7th of November 1997, prohibits the use of any substance in any form or manner (except as otherwise provided by law), including the establishment or distribution of narcotics. The ban also includes recreational and illegal substance use (Roshanpajouh et al., 2020). Substance use has been a long-standing challenge in the field of social and public health in Iran and the prevalence of drug use is increasing despite decades of struggle against drug use (Roshanpajouh et al., 2014; Saberi Zafarghandi et al., 2014). Although many studies have attempted to provide estimates of the prevalence of substance use, there is no accurate and reliable information in Iran (Roshanpajouh et al., 2020). After the Islamic revolution, alcohol consumption became illegal, making it difficult to estimate the burden of alcohol SUD (Kabir et al., 2016; Amin-Esmaeili et al., 2017, 2018). The first Rapid Assessment Response (RAR) study in 1999 by the State Welfare Organization in 10 provinces of Iran showed the substance dependency of a million individuals (Razzaghi et al., 1999).

All the mentioned RAR studies have used snowball sampling or hospital referees and qualitative methods to estimate the prevalence of SUD. Therefore, there are uncertain estimates due to methodological methods. The national survey on SUDs in Iran, conducted in a sample of 15,000,000 people in 10 provinces, showed that the number of ever life substance users is about 1,352,000 (United Nations Office on Drugs and Crime (UNODC), 2010). According to Iran's Forensic Medicine Organization in the years 2009-2011, after road accidents, the second cause of abnormal death was SUD. This organization suggests that 10 people die every day due to SUD (Mohammadi et al., 2013). The findings of a national survey to examine the attitudes of people toward SUD in Iran have shown that the biggest concern of society is the distribution of substances among young people (Hajli et al., 2010).

The substance use survey in Afghanistan showed a prevalence of 3.8% of the total population in the past month in 2005 (UNOCD, 2010). In the study of Roshanpajouh et al. (2020), opium was the most prevalent substance use, followed by cannabis and heroin. In this line, Iran opium

consumers use 42% of the total opium in the world but in the western countries, marijuana is the most prevalent substance used (SAMHSA, 2017). It is of note that due to Afghanistan's geographical proximity to Iran (as the world's largest opium producer), opium is the most prevalent substance in Iran (Roshanpajouh et al., 2020).

The substance use survey in Afghanistan showed a prevalence of 3.8% of the total population in 2005 (UNODC, 2010), which is similar to the findings of Roshanpajouh. In the study of Roshanpajouh et al. (2020), opium was the most prevalent substance use, followed by cannabis and heroin. In this line, Iran opium consumers use 42% of the total opium in the world but in the western countries, marijuana is the most prevalent substance used (UNODC, 2010). It is of note that due to Afghanistan's geographical proximity to Iran (as the world's largest opium producer), opium is the most prevalent substance in Iran (JafariKhounigh et al. 2014; Roshanpajouh et al., 2020).

The type of substance use varies according to the cultural and social structure of each society (Rastegari et al., 2013). Sarrami et al. (2013) concluded that the most commonly used substances among students were nicotine, hookahs, and opium, in the order of their appearance. In another study, opium use had the highest consumption in addicted people among other substances (JafariKhounigh et al. 2014), while being about 2.3% in students (Taremian et al., 2008). In an epidemiological study of the mortality rate from SUD in Iran on 2306 died cases from SUD, it was reported that the most mortality rate from SUD was among unmarried young men (30-39 years) with low education and also a low level of self-employed (Ghoreishi et al., 2017). Table 2 presents a selection of reviewed conducted studies on the substance used population in Iran between 2012 and 2020.

Table 2. Rate of substance use among SUD (substance use disorder) patients in some published works in Iran from 2012 to 2020.

Shekarchizadeh et al. (2012)	A study on 810 addicted showed that opium use was (92%), while for other drugs, heroin, cannabis, and amphetamine, it was 33%, 28%, 16%, and 15%, respectively.
Baheiraei et al. (2013)	The rate of alcohol use in big cities like Tehran-Iran and Kerman-Iran (1.1%) were reported to be more than small cities; i.e., 15.5% and 11%, respectively.
Holakouie-Naieni et al. (2015)	The prevalence of substance use in different cities from 120 studies was 16.4%.

Ghoreishi et al. (2017)	A study on 2,306 addicted patients showed that opium use was up to 37.3%, the crystal was 24.63%, heroin was 21.34%, and the crack was 9.93%.
Vakilian et al. (2019)	About 20% of students had experienced tobacco smoking, while 33% and 7% had experienced alcohol and substance use, respectively. Nearly, 14% of females and 22% of male students had a history of tobacco smoking.
Roshanpajouh et al. (2020)	In the largest survey of substance use in Iran, the prevalence of permanent use of substances was 8.5%; and for the past week, drug use was 4.3%.

Opium consumption rate is the highest in the Middle East and South-West Asia, especially in Malaysia, Macau, and China. The estimated number of people who used substances at least once was the highest among Asians, Europeans, Americans, and Africans respectively (UNODC, 2010). Iran ranks third in the prevalence of illicit substance use among the population aged 15-64 years in the Middle East. Except for cannabis, the prevalence of all types of substance use in the Middle East is higher than worldwide estimations (WHO, 2017). Among all European countries, England, Latvia, Italy, and Spain had the highest prevalence rate of all substances among the age of 15-64 years, in the order of their appearance (Torrens et al., 2015).

The start of substance use during early youth has been related to a higher risk of later abuse in life (Warren et al., 2017). Moreover, it has been found that high caffeine users are more prone to use other substances, especially nicotine (Owens, 2014). For example, in a study, it was reported that people who use cannabis are more prone to use other substances like alcohol, tobacco, and other illicit drugs (Caviness et al., 2015). In a recent study on 317 SUD patients, the majority of them reported the cocaine as their first choice, and one-third preferred alcohol (Pillon et al., 2019). Cocaine use is also reported as the main substance among SUD patients in a recent study (Daigre et al., 2019). Thus, people with more severe substance use referring to SUD treatment may have stated less remission in mental health at follow-up sessions (Bootzin & Stevens, 2005). For instance, it has been indicated that among SUD patients, those with higher severity of alcohol SUD and cannabis use could not complete the treatment sessions while cocaine users completed it more frequently (Daigre et al., 2019). Up to 62% of youth and 95% of adolescents who refer to residential treatment centers reported at least one psychiatric or mental diagnosis (Bootzin & Stevens, 2005). Therefore, SUD usually co-occurs with other mental diseases (Bootzin & Stevens, 2005; Conroy & Arnedt, 2014; Daigre et al., 2019). Since substance use can cause mental illness and vice versa and both are caused by other risk factors, covering genetic vulnerabilities, overlapping environmental activates, the contention of related brain regions, and reviewing them

as developmental disorders are some important factors that lead to comorbidity (Torrens et al., 2017; Miesch & Deister, 2019).

1.5.1. Dual disorders

A growing interest has emerged in the comorbidity between SUDs and other mental disorders in psychiatry and psychology within the past few decades (Teesson & Proudfoot, 2013; Adan et al., 2017a; Torrens et al., 2017; Daigre et al., 2019). The term 'comorbidity' was introduced in medicine by Feinstein (1970) and it is commonly used to refer to the overlap of two or more psychiatric disorders. Here, when two disorders occur in the same person simultaneously, they are called comorbidities. Comorbid circumstances with SUDs and mental disorders are very frequent (Drake & Mueser, 2000; Buckley, 2006; Lechner et al., 2013; Teesson & Proudfoot, 2013; Jones & McCance-Katz, 2019) and related to larger illness development, chronicity, and deterioration (Balanzá-Martínez et al., 2015). Individuals with SUD comorbid psychiatric illness have higher rates of psychiatric hospitalizations (about 20-50%) (Gut-Fayand et al., 2001; Lubman et al., 2010), suicide attempts (Adan et al., 2017c), more social problems, and more delinquent behaviors than those without comorbidity (NIDA, 2007; Torrens et al., 2017).

Scientific interest in dual disorders (DD) is based on the observations made in clinical samples, according to which the patients with both SUD and mental disorders are clinically more severe and treatment-resistant than the patients with only one disorder (Kessler, 2004; Margolese et al., 2006; Jones & McCance-Katz, 2019). In population-based surveys, the lifetime prevalence of DD was found to be 18-50% with higher rates being in clinical samples (Weaver et al., 2003; Kessler, 2004; Bizzarri et al., 2009). For instance, a study on a clinical sample in Spain found prevalence rates of 43.9% for SZ and Schizophreniform disorder, 16.3% for MDD, and 14% for BD among patients with a SUD (Rodriguez-Jimenez, 2008). A recent study by Jones & McCance-Katz (2019) reported that the prevalence of comorbidity of SUD in patients with past mental illness and serious mental illness was 64.3% and 26.9%, respectively. The term DD or dual pathology (DP) was used for a broader meaning since it is very difficult to establish whether drug consumption and the other psychiatric disorder are independent entities or not (Torrens et al, 2011). Three main reasons explained the impossibility of establishing causality for DDs and the difficulty of elucidating which disorder was developed earlier. First, emotional and behavioral problems may not be so

severe for diagnosis. Second, mental health problems may trigger substance use. Third, one's reminders may be incomplete from the first substance use (Gust & McCormally, 2018).

The clinical characteristics shown by patients with DP make it a topic of interest for both researchers and mental health professionals. DD is commonly linked to multiple clinical features that demand a multidisciplinary approach from the psychopathological, medical, and social perspectives. Several main ways can contribute to the comorbidity of substance use and mental disorders. Common risk factors such as genetic vulnerabilities, epigenetic and environmental influences, brain region involvement, stressors, and traumas in childhood, and mental disorders may contribute to SUDs can contribute to both mental disorders and SUDs. Moreover, SUDs may contribute to initiating a mental disorder (NIDA, 2007, Gust & McCormally, 2018). According to several studies, compared to the patients with a single diagnosis, DD patients are prone to adverse clinical characteristics, present a poor prognosis, usually have a high number of addiction relapses (Weaver et al., 2003; Kessler, 2004; Olivares et al., 2013; Antúnez et al., 2016; Adan et al., 2017a, Marquez-Arrico et al., 2019a), and have more polydrug use (Rodriguez-Jimenez et al., 2008; Casares-López et al., 2011; Marquez-Arrico et al., 2019b) compared with the patients who only have SUD (Luna & López-Delgado, 2006). Among other characteristics, DP is related to worse QOL (Benaiges et al, 2012; Eaves et al., 2017; Lee et al., 2020), more neuropsychological deterioration (Benaiges et al., 2013b), lower social support consultation (Marquez-Arrico et al., 2019b), and lesser use of social support (Marquez-Arrico et al., 2015).

In terms of personality disorders, it has been revealed that SUD is often correlated with the antisocial and borderline disorder (Torrens et al., 2017). For instance, younger adolescents showed higher frequencies of comorbid psychiatric disorders and a higher risk of self-injury. Moreover, those with physical and sexual childhood abuse, also report higher levels of substance use and problems related to higher rates such as anxiety, depression, ADHD, hyperactivity, anger, and aggression (Bootzin & Stevens, 2005). Personality traits such as high impulsivity and high sensation-seeking can be considered as endophenotypes of addiction since they are present in a premorbid way and are an indicator of great specific weight in the vulnerability to develop a SUD (Zhornitsky et al., 2012; Adan et al., 2017d). An ancient association between DDs and impulsivity was reported in a study conducted by Verdejo-García (2008). According to this association, impulsivity may occur due to chronic exposure to substances, which may incur harmful effects on

the brain. Moreover, impulsivity may even precede SUDs (Perry & Carroll, 2008; Ersche et al., 2010). This association is a trait that explains a part of the process of vulnerability against the use of drugs, consumption patterns, and progression toward addiction (Belin et al., 2008). Ineffective management strategies to deal with stress in SUDs are strongly related to their severity of addiction (Stappenbeck et al., 2015). In this case, when SUD patients encounter a new problem situation, those with a limited strategy for coping are more prone to turn to substance use than those who use a stronger mechanism of strategy. They use substances to deal with negative emotions and stress (Blevins et al., 2014). A recent study has shown that incompatible strategies to cope with problems in DDs are more than to patients with only SUD diagnosis (Marquez-Arrico et al., 2019a). It has recently been observed that social support has an important effect on the improvement of QOL of alcohol SUDs with psychiatric symptoms (Lee et al., 2020).

1.5.2. Substance Use Disorder comorbid Schizophrenia

SZ is a complex mental disorder that has the most severe and destructive impact on one's life. The prevalence of this disorder is reported to be about 1%. SZ is categorized by positive symptoms, such as delusions, abnormal motor behavior, disorganized thoughts, and hallucinations. On the other hand, it has negative symptoms such as flattened affect, social withdrawal, and lack of enthusiasm and interest, alogia (reduced speech productivity), and anhedonia (diminished capacity to experience pleasure) during a period of one month or longer (APA, 2013). The word Schizophrenia was introduced more than 100 years ago by Bleuler to explain the separation or splitting of the mental functioning of SZ patients (Fusar-Poli & Politi., 2008; Ferrarelli, 2015). The age of onset of SZ is from adolescence to adulthood and the cause of it remains unknown (National Institute of Mental Health (NIMH, 2014). Twin studies and having a family with a history of psychosis in a third of SZ patients helped create a hypothesis that inherited genetic risk factors playing an important role in the manifestation of SZ (Sullivan et al., 2003; Lawford et al., 2005; Hoenicka et al., 2006; Owen et al., 2010).

Psychiatric disorders such as SZ are risk factors in increasing the use of substances. They also increase the development of a SUD that might continue even after treatment or remittent of psychiatric disorder (NIDA, 2007). Nearly 50% patients with SZ experience a lifetime history of SUD (Talamo et al., 2006; Lubman et al., 2010; Torrens et al., 2017), at least three times more

than the general population, especially in alcohol SUD (Sara et al., 2014). This comorbidity and multiple substance use (polydrug use) are common among these patients (Lubman et al., 2010), around 30-66% (Green, 2005). Thus, SUD comorbid schizophrenia (SUD+SZ) has been one of the most studied DD (Sara et al., 2014; Adan et al., 2017a, c).

Assumption of self-medication in SZ patients suggested that the use of substances is an endeavor to deal with their symptoms (Teesson & Proudfooot, 2013) or substance use could be an effort to attenuate early prodromal symptoms (Gut-Fayand et al., 2001). High prevalence of substance use in patients with SZ happens together with self-medication to diminish negative symptoms, such as blunted affect, apathy, anhedonia, depression, or antipsychotic side effects, and also to decrease positive symptoms such as hallucinations and delusions (Mueser et al., 1998; Talamo et al., 2006; Lubman et al., 2010; Teesson & Proudfoot, 2013). Reasons for self-medication include reluctance to social relatives, absence of emotion or feeling for others, lack of energy, sleeping difficulty, depression, anxiety, agitation, tremors or shaking, and boredom (NIDA, 2007). SUD+SZ patients are reluctant to treatment or long-term treatments compared to patients without such a disorder (Brunette et al., 2016). It has been suggested that the use of a substance in psychotic patients may be the result of rejecting the severity of their illness or is a potential benefit of medical interferences, which may reduce the time seeking treatment after the onset of psychosis (Norman & Malla, 2002).

One of the most important risk factors in suicide attempters in SZ patients is comorbidity with substance use (Adan et al., 2017c; Østergaard et al., 2017). A recent review by Adan et al. (2017a) about neurocognitive underpinning suggested that SUD+SZ patients may have poorer general executive functioning, as well as weaker abilities and problem-solving skills. This comorbidity is a risk factor in relapsing, hospitalization, and higher mortality than what is observed in the two disorders alone (Brunette et al., 2016). Besides, SUD+SZ patients showed worse social functionality in comparison with SUD patients (Adan et al., 2017c). A recent study reported that SUD+SZ patients use less frequently problem-solving, self-criticism, and social support strategies and also employ less compatible strategies to adapt to problems compared to the patients with only SUD (Marquez-Arrico et al., 2019a).

Cannabis SUD (especially cannabis abuse) and, with less evidence, cocaine may precede quick psychosis, especially in young patients (Talamo et al., 2006; Torrens et al., 2017). Cannabis use leads to poor treatment consequences for psychotic patients (Kelly et al. 2013). A high dose of substance use can produce a psychotic disorder (NIDA, 2007) and exacerbate the positive and negative symptoms of SZ (Bennett et al., 2009). It has been reported that positive symptom scores in SUD+SZ patients were higher and negative symptom scores were lower compared to SZs (Talamo et al., 2006). In this line, a significant relationship has been reported between suicide risk and positive symptoms in SUD+SZ patients (Adan et al., 2017c). In a recent study, severe mental illness (SZ and MDD) patients showed higher negative symptoms than DDs (Marquez-Arrico et al., 2019a). However, Uludag & Güleç (2016) did not detect any significant difference in the positive and negative symptoms of SUD+SZ and SZ patients.

Despite the high incidence of comorbid SUD+SZ, the information about the influence of substance use on psychosis is limited (Wobrock et al., 2013) although reporting that the use of substances may increase the risk of psychosis onset (Smit et al, 2004; Semple et al, 2005). Male gender, low literacy, family history (Cantor-Graae et al., 2001; Westermeyer, 2006), being younger, availability of drugs, and increased vulnerability of patients with SZ and neurobiological factors have been stated as the most common causes for SUD+SZ (Addington & Addington, 2007; Dervaux et al., 2010a, b; Patel et al., 2016). In this regard, there is a strong relationship between SUD and an earlier age of onset of SZ (Barnes et al., 2006; Donoghue et al., 2014) compared with the SZ group. Younger age was related to more cannabis SUD whereas older age was associated with alcohol and polydrug use (Brunette et al., 2018). A recent study reported that in the onset age of SUD and mental illness, DDs showed the earliest ages in comparison to SUDs and severe mental illness group (Marquez-Arrico et al., 2019a). The first study to examine the effect of age variation in association of cannabis use and cannabis use disorder with psychotic symptoms was conducted among 662 adolescents in Victoria, (British Columbia, Canada) during 10 years and the second phase from the United States in 36,309 adults in 1 year. The results showed that psychotic symptoms were more in adolescents and decreased steadily with age; moreover, cannabis SUD was associated with psychotic symptoms after age 23 years (Leadbeater et al., 2019).

In Germany, Wobrock et al. (2007) stated that the risk of developing SZ is increased in those consuming cannabis recreationally and those using it continuously. Moreover, they found a strong

relationship between hashish use and early onset of psychosis. In an Iranian study by Behdadi & Habrani (2011) in SUD+SZ patients, it was reported that 50% of those with a history of substance use had the onset age under 25 years. Uludag & Gülec (2016) reported that among SUD+SZ and SZ patient groups, SZ, drug use, and alcohol use were more common in men and that SUD+SZ patients had more side effects of drugs, psychopathology symptoms, and multiple substance use than SZ patients.

Nicotine use in SZ patients is about 3 times higher than among the normal population (Mancini-Marïe et al., 2006; APA, 2013). Several hypotheses have been proposed for the high consumption of nicotine in psychotic patients, such as common genetic factors that predispose a person to both psychosis and nicotine use, self-medications for reducing symptoms and side effects of drugs, and environmental factors such as stress (Kalman et al., 2005).

Differences in the usage of substances between Iran and other countries can be related to cultural issues and the availability of these substances (Bahdani & Habrani, 2011). So far, limited studies have been conducted on DDs, especially SUD+SZ. A study conducted in Iran on 100 SUD+SZ patients reported that around 74% of them were nicotine, opium, or cannabis users and 47% of them had a history of psychiatric disorder in their family (Bahdani & Habrani, 2011). The current study reported multiple substance use in women, especially nicotine and opium. However, in other studies, the most substance use in women was reported to be cannabis and nicotine (Cantwell, 2003). In 2004, in Turkey, the rate of nicotine use in SZ patients was observed to be between 50-76% (Akvardar et al., 2004). In Uludag & Gülec (2016), the rate of nicotine use in SUD+SZ patients was around 70%. In another study, Barnes et al. (2006) observed that among SUD+SZ patients, cannabis/psychostimulants together and alcohol use with 68% and 27% were the most substance used, respectively. Furthermore, Torrens et al. (2015) reported in Poland that the most commonly used substances in SUD+SZ patients were cannabis, amphetamine, and alcoholic beverages, in the order of their appearance, but in Spain, DDs reported more cocaine and alcohol use compared to SUDs (Marquez-Arrico et al., 2019a).

Hypothetically, a part of the brain in SZ patients has dysfunctional dopamine affliction, and this part is rewarded with the use of the substance (Green et al., 2007). Therefore, dysfunction within the brain's reward system and frontal executive deficits may play an important role in SUD+SZ

patients (Lubman et al., 2010). The SUD+SZ patients scored higher than SZ patients without SUD on impulsive and unplanned activity, which has been linked to a higher rate of suicide attempts (Gut-Fayand et al., 2001; Suokas et al., 2010), more prominent positive psychotic symptoms (Talamo et al., 2006), increased risk of being offended (Fazel et al., 2009), and more criminal activities and violent behaviors (Strakowski et al., 1996; Uludag & Gülec, 2016). Since the SUD+SZ patients are more prone to withdraw treatment and the follow-up sessions, they show slower improvement in the treatment process (Horsfall et al., 2009). Even with the follow-up of a treatment and with years of recovery and remission compared with SUD or SZ patients, SUZ+SZ patients are at increased risk of relapse and recurrence (Xie et al., 2005). Recently, Stompe et al. (2018), using Structured Clinical Interview for DSM Disorders (SCID), researched the impact of substance use in 432 men including healthy with and without offensive behavior and SZ patients with and without offending behaviors. SZ with and without offending behavior as well as healthy offenders were characterized by higher rates of alcohol and illicit drug abuse. Multiple substance use was related to lower aggression and illegal behavior. The highest rate of SUD was observed in SZ offenders, even if no association was found between the patterns of substance use and the severity of offending behavior. SZ patients without offending behavior also indicated a high prevalence of illicit drug use, especially cannabis.

Kerner (2015) investigated 1,219 individuals with 50% history of SUD and 30% history of SZ in their families. They concluded that SUD preceded the beginning of SZ in about two-thirds of cases and SUD was related to more severe problems in cognitive and social abilities. Wobrock et al. (2013) observed very similar cognitive functioning and psychopathology in SUD+SZ and SUD patients. They only revealed decreased verbal memory performance and pronounced damages in memory function in older SUD+SZ patients. The results indicated that cognitive deficiencies in substance users happen after long and high use. Marquez-Arrico et al. (2019a) in the first study that compares coping strategies on 223 patients including DDs, SUDs, and severe mental illness disorders reported that one's strategy to cope with problems depends on the presence or absence of SUD. Meanwhile, DDs and SUD patients reported more self-blaming, guilt, and problem avoidance in facing difficulties. In this context, social support was an important issue sociated with addiction relapses in a one-year follow-up. Moreover, DDs reported more suicide attempts in comparison to SUD and severe mental illness patients.

A study conducted among 403 Moroccans patients with SZ with and without cannabis use showed that cannabis users were younger. In terms of gender, SZ patients without cannabis use were more male and they reported more history of imprisonment and poorer medication adherence. They did not find any significant difference between cannabis users and non-users in the type of SZ, the number of hospitalization, and medication type. Also, SZs who reported cannabis use showed lower age of onset of SZ disorder than non-users. The study interpreted the early onset age of SZ in two ways: 1) whether cannabis use stimulates the SZ symptoms for people with a genetic predisposition and 2) whether the early age of onset of SZ can lead to self-medication or overcoming the disorders. There are three risk factors related to cannabis use among SZ patients; male gender, history of imprisonment, and non-adherence to medication (Bouri et al., 2020). Brunette et al. (2018) have researched 404 patients with first episodes of SUD+SZ. They did not find any relationship between SUD and onset age of psychosis, but they found a lifetime of SUD related to the male gender and white race. One-half of SUD patients met the criteria for any lifetime of alcohol or drug use disorder. A cross-sectional work with 492 DD patients in Iran-Sari indicated that SUD was related to the male gender, urban area, illiteracy, and cigarette smoking (Habibisaravi et al., 2015). Opium use with/without other substances was the most substance consumption among DD patients (up to 67%). The results of the research on this scope from 2006-2020 are shown in Table 3.

Table 3. Characteristics of patients with substance use disorder (SUD) comorbid to schizophrenia (SUD+ SZ). A revision of the works published from 2006 to 2020.

Author	**Sample**	**Measure**	**Main Results**
Barnes et al. (2006)	N = 152 (men: 110) 16-50 yrs. SUD+SZ=84 SZ = 26	SURSp, CGI, SAPS, SANS, CPRS, Social Function Scale	Men had more SUD. The earlier onset age of psychosis in SUD+SZ patients was found. Cannabis was the most widely used substance.
Talamo et al. (2006)	N = 725 34.9 ± 6.9 yrs. SUD+SZ = 340 (34.9±6.9 yrs) SUD-SZ = 385 (35.9 ± 6.4 yrs)	WMH-CIDI, CCHS 1.2	In SUD-SZ, higher PANSS scores were significantly associated with younger age. Total PANSS scores did not vary between these subgroups. SUD was more common in male SZ patients and they used more alcohol, cannabis, and cocaine. SUD+SZ group showed more PANSS positive scores.

Ghaffari Nejad et al. (2009)	N = 192 Sex not specified 33.92 ± 7.67 yrs.	SCL-90, GSI,	Heroin users reported more DD including obsession-compulsion, anxiety, phobia, and psychosis than opium users.
Behdani & Habrani (2011)	N = 100 (men: 68) SUD+SZ 15-78 yrs.	Self-questionnaire	Most of the substance users (92%) were men. In men, the highest used substance was nicotine and in women, it was nicotine and opium.
Schmidt et al. (2011)	N = 107 (SUD+SZ) N = 119 (SZ) 19-89 yrs. (men: 163)	Self-questionnaire	SUZ+SZ patients had more hospital contacts, more hospitalization, and more risk of dying during the follow-up sessions than SZ patients.
Habibisaravi et al. (2015)	N = 492 (men: 385) 39.9 ± 11.9 yrs.	Structure interview	Opium use with/without other substances was the most substance use (up to 67%) among patients. SZ and BD were the most comorbid disorders in patients. The onset of SUD started approximately 2 years after beginning the smoking. SUD was more prominent in the male gender, urban area, illiteracy, and cigarette smoking.
Uludag & Gülec (2016)	N = 100 (men: 67) 32-51 yrs. N = 35 (SUD+SZ) N = 32 (SZ)	SCID-1, Brief disability questionnaire, AUDIT, SAPS, SANS, Insight rating scale, GAF	In men, more drug and alcohol use were observed. SZs had more disability and psychopathology. The functioning of SUD+SZ patients was worse than SZs. Also, they did not find any significant relationship between substance use and marital status. Moreover, there was not a relationship between education and alcohol use in the two groups.
Adan et al. (2017c)	N = 50 (only men) 36.06 ± 7.79 yrs. N = 24 (SUD+SZ+suicide attempters) N = 26 (SUD+SZ-suicide attempters)	PANSS, CGI-S, SASS , BDI , RS , DAST-20 , GAF	In terms of sociodemographic data and psychosis symptoms, no significant difference was observed between groups, length of abstinence, the number of relapses, duration of SUD, and severity. Higher sizes of patients with suicide risk, higher SUD, and SZ in first-degree relatives of patients, higher alcohol and nicotine consumption, and worse general executive functioning with low performance in problem-solving skills were observed in SUD+SZ+suicide attempted group.
Stompe et al. (2018)	N = 432 total (only men) N = 103 (SZ+offensive behavior) 31.4 ± 9.0 yrs. N = 103 (healthy offensive behavior) 34.6 ± 10.4 yrs. N = 103 (SZ non-offensive behavior) 30.8 ± 6.3 yrs. N = 103 (healthy non-offensive behavior) 33.6 ± 8.1 yrs.	SCID, Categorical, classification of Taylor	Only a few numbers of the healthy participants reported a lifetime history of total substance abuse. Both offender groups showed high rates of comorbid substance abuse. Except for the group of SZ non-offenders, the other three groups showed significantly higher rates of substance abuse among all types of uses. The highest prevalence of only illicit drug abuse was found in the group of SZ non-offenders. No association was found between the pattern of substance use and the severity of the offensive behavior. A higher prevalence of substance use is related to both psychiatric illness and criminal behavior. The effect of substance use on the form of criminal behavior was very similar in healthy and SZ criminals. Illicit substance use alone was not

			a strong predictor of criminal behavior, but the combination of illicit drugs and alcohol seems to stimulate offending behavior especially in SZ patients.
Brunette et al. (2018)	N = 404 (men: 293) SUD+SZ 15- 40 yrs.	SCID, PANSS, CDSS, QLS, Stigma scale	Gender, race, and excited symptoms were the most obvious predictors of lifetime SUD. Half of first-episode SZ has co-occurring SUD. Younger age was related to cannabis abuse whereas older age was correlated with alcohol and multiple SUD. SUDs tended to have less impaired cognitive functioning than those without these disorders. No relationship was observed between substance use disorders and the onset age of SZ.
Thomas et al. (2018)	N = 320 18-60 yrs. SZ = 105 BD: 57 Relatives of SZs = 87 Control= 87	CSM, GAF, AAO	Gender was not different across the groups but age was significantly different among SZ, first-degree relatives of SZs, bipolar patients, and control groups. Controls were significantly younger compared to the relatives of SZs. SZs and bipolar patients were more likely to be ET.
Leadbeater et al. (2019)	N= 662 adolescent data (men: 320) N= 36,309 adults data (men: 13,761)	Mini interview, SCL-90	Psychotic symptoms were reported at the maximum levels and decreased steadily with age in adolescents. Cannabis SUD was associated with psychotic symptoms after age 23 years.
Marquez-Arrico et al. (2019a)	N = 233 39.11 ± 8.45 yrs. SUD+SZ= 39 SUD = 43	SCID, DAST-20, PANSS, CSI, HAMD-17	The age of onset of SUD and severe mental illness in DDs was earlier. The most prevalent substance use in DDs was cocaine, alcohol, and polydrug use. The DDs had higher scores in self- criticism, lower score in problem avoidance, lower social support, and more self-blaming in comparison to the severe mental illness group. The highest relapse of addiction unmanaged was in DDs. DDs showed more suicidal attempts in a 1-year follow-up. Social support appeared to have a protective value for DD patients with SZ.
Bouri et al. (2020)	N = 403 (men: 363) Cannabis use = 190 33.3 ± 9.1 yrs.	PANSS, GAF,CDSS, MARS, BIS-10	Cannabis use in SZs was around 50%. Cannabis users were younger, mostly men, and with more history of imprisonment. Cannabis users reported a lower age of onset and poorer medication adherence compared with non-users. No significant difference was observed between cannabis users and non-users in the number of hospitalization and type of medication.

AAO (Age at onset index); ADCQ (Alcohol and Drug Consumption Questionnaire); AUDIT (Alcohol Use Disorders Identification Test); BACS (Brief Assessment of Cognition in Schizophrenia); BDI (Beck Depression Inventory); BIS-10 (Barratt Impulsiveness Scale); BIS-11 (Barratt Impulsiveness Scale-11); CCHS (Canadian Community Health Survey); CDSS (Calgary Depression Scale for schizophrenia); CGI (Clinical Global Impression); CGI-S (Clinical Global Impression-Severity scale); CPRS (Comprehensive Psychopathological Rating Scale); CSI (Coping Strategies Inventory); CSM (Composite Scale of Morningness); DAST-20 (Drug Abuse Screening Test-20); GAF (Global Assessment of Functioning); GSI (Group Styles Inventory); HAM-17 (Hamilton Depression scale); MARS

(Medication Adherence Rating Scale); PANSS (Positive and Negative Syndrome Scale); QLS (Heinrichs-Carpenter Quality of Life Scale); RS (Plutchik Risk of Suicide Scale); SANS (Scale for the Assessment of Negative Symptoms); SAPS (Scale for the Assessment of Positive Symptoms); SASS (Self-Evaluation Scale); SCID (Structured Clinical Interview for DSM Disorders); SCL 90 (Symptom Checklist 90); SURSp (Substance Use Rating Scale-patient version); WMH-CIDI (World Mental Health Composite International Diagnostic Interview).

1.5.3. Substance Use Disorder comorbid Major Depressive Disorder

In DSM 5, unlike its previous version (DSM-IV), MDD was classified in "depressive disorders" as one of the most prevalent psychiatric illnesses. The diagnosis considers five or more symptoms during two weeks including 1) depressed mood, 2) loss of interest, 3) insomnia or hypersomnia, 4) psychomotor agitation or retardation, 5) guilty feeling, 6) problems in concentration, 7) thought or death or suicidal ideas, 8) fatigue or loss of everyday energy, and 9) feeling of worthlessness (APA, 2013). In addition to the decreased energy levels and apathy (Robillard et al., 2014), depression results as the patients quit fighting in their lives, leading to the feeling of being surrounded by limitations and outside difficulties that have been also considered (Lester, 2015). Depression is a frequent disorder that has high morbidity and mortality (Chan et al., 2014), independent of cultural context. Its statistics in Canada, Europe and the Unites States are 8.2%, 8.6%, and 8.7%, respectively (Levandovski et al., 2011). In this respect, there are some critical factors to the emersion of this disease including depression in a parent, family history of depression, the loss of a loved one, or environmental stress such as physical or sexual abuse (De Souza & Hidalgo, 2014).

There are many reasons for the difference in the dependence level of MDDs on SUDs. For example, MDDs contain symptoms relating to low motivation (e.g. anhedonia, which is the loss of interest or pleasure in activities previously enjoyed) and psychomotor retardation (i.e., not having the energy to find substances or not having experienced symptoms that motivate people to use substances). Therefore, MDDs with anhedonia may use substances since they are impotent to enjoy normal activities (Kalechstein et al., 2002; Leventhal et al., 2008). In this line, MDDs with more activation (including psychomotor agitation and/or insomnia) may look for substances to self-medicate those symptoms (Wadsworth et al., 2005; Keller et al., 2007). A recent study on cannabis SUD indicated a 92% improvement in depressive and/or anxiety symptoms of drug users by cannabis use (Turna et al., 2019).

A great body of research has indicated that substance use can exacerbate depression (Wulff et al., 2010; Levandovski et al., 2011; Torrens et al., 2017; Pillon et al., 2019). Severe alcohol drinking in addicted and non-addicted persons can cause depression (Wulff et al., 2010). Also, the presence of an MDD increases the likelihood of developing a SUD and vice versa (Blanco et al., 2012; Cornoy & Arnedt, 2014). Adolescents and adults with depression history may experience exacerbated symptoms if they begin or continue to use substances, especially cannabis (Leadbeater et al., 2019). This comorbidity leads to poorer diagnosis (Vujanovic et al., 2017) with more mortality and treatment costs (Compton et al., 2007; Clark et al., 2009; Mojtabai et al., 2014).

Throughout the prenatal period, substance use impairs fetal growth that subsequently increases the risk of diseases in later life such as depression (Kaminer et al., 2007). MDD is the most common disorder among psychiatric comorbidities in individuals with SUDs (Sepehrmanesh et al., 2014; Mortazavi et al., 2015). In other words, in depressed patients, the comorbidity is higher than other psychiatric disorders (Pirkola et al., 2005; Kessler & Bromet, 2013; Pillon et al., 2019) with the prevalence of 36% in men and 16% in women (Hunt et al., 2020). The relationship between SUD and depression is clear (Pillon et al, 2019). One-fourth of MDD patients suffer from a comorbid alcohol use disorder as well. Familial and genetic factors seem to be two risk factors for comorbidity of SUD and MDD (SUD+MDD) (Paavonen et al., 2016). In a recent study conducted among 307 SUD patients, 71% of the patients were diagnosed as depressed (Pillon et al., 2019). In individuals with alcohol SUD, depressive disorders are more frequent (Logan et al., 2014). Although a recent study, no significant difference in gender was observed among SUD+MDD patients (Levola et al., 2020). Other studies denoted that among individuals with a SUD, MDD is more common in women than in men (Bootzin & Stevens, 2005; Torrens et al., 2017). Zhou et al. (2019) investigated 106,142 women patients with MDD/anxiety disorder from 2008 to 2014 and reported that MDDs and/or anxiety disorder had a higher prevalence of substance use and SUD compared with ones with no MDD or anxiety disorder. In this study, a majority of patients with SUD did not receive any treatment, especially alcohol users; also, in women with MDD or/ and anxiety disorder, the prevalence of tobacco, illicit drug use, and SUD in the past 2-12 months was higher than the women without SUD. Less than a quarter of patients with SUD, MDD, and anxiety disorder received treatment for substance use and mental health.

In the study conducted in the United States, the incidence of MDD in SUD individuals in the previous 12-months ranged from 8% for alcohol use to 40% for all drugs (Currie et al., 2005). A survey study conducted in Thailand on 17140 individuals with depression using Mini International Neuropsychiatric Interview (MINI) reported that individuals with SUDs, especially alcohol, had a significantly increased risk of MDD compared with the general population (Suttajit et al., 2012). A recent systematic review of MDD patients from 1990-2019 reported that comorbidity with SUD is highly prevalent and has not changed over time (Hunt et al., 2020). More SUD dependence was reported in those with more comorbidities. Back pain, hypertension, and liver disease were the most frequently observed pathologies in SUD+MDD patients (Levola et al., 2020). Vidaña et al. (2020) in a study on 193 patients with/without posttraumatic stress disorder (PTSD) or MDD comorbid SUD reported comorbidity of PTSD and SUD with more risk-taking behavior and recurrent MDD may moderate this association.

In Iran, depression among men with SUD seems to be more frequent than among women (Hojjati et al., 2010; Sepehrmanesh et al., 2014; Mortazavi et al., 2015). In a study conducted in Iran by Akbari & Amoupour (2013) on 210 students using the Beck Depression Inventory (BDI), it was reported that boys had a more tendency to SUD than girls. In this study, higher depression scores were correlated with more addiction attitudes. Moreover, they found that being a woman with low educational grade increases the risk of depression. Depression and disappointment play a key role in the QOL and a tendency to substance use of adolescents (Servatyari et al., 2019). Among SUD patients, the higher severity of depression was associated with both poorer self-rated health and QOL and more comorbidities than non-depressed ones (Levola et al., 2020). A positive relationship between depression and disappointment and smoking history also was reported by Servatyari et al. (2019). In this sense, Mohammad Nia & Mashhadi (2018) reported a significant negative relationship between depression and the meaning in life and between the meaning of life and attitudes toward substance use in the Iranian population. They suggested a two-way connection between depression and the meaning of life. Depression was caused by a variety of factors that can reduce the meaning of life, and this destructive feeling can lead to substance use. According to these data, patients with alcohol SUD with both high QOL and social support reported lower depression. Therefore, social support has an effective role in improving alcohol SUD patients (Lee et al., 2020).

A study among Australian teenagers revealed that more frequent cannabis use predicted about double the increased risk of later depression (Patton et al., 2002). In a survey study on the United States in 2018 on 9,272 high-school seniors in the association between cannabis use and depressive symptoms, it was reported that cannabis use was not generally related to depressive symptoms. Approximately 8% of high-school seniors reported cannabis use in the last 12 months and 24% reported high depressive symptoms. Besides, 33% of students reported low levels of depressive symptoms and 24% reported a high level of depression. Cannabis and illicit drugs were associated with medium and high depression. Cigarette smoking is associated with high and alcohol use related to low levels of depression (Ihongbe et al., 2018). To examine the strength of age varying associations of cannabis use and cannabis SUD with depressive symptoms, a recent study was conducted among adolescents in Victoria, British Columbia, Canada for 10 years and adults in the United States for 1 year. The results indicated that symptoms of depression and anxiety gradually increases until age 18 years and then persists. Cannabis use disorder was associated with more depression at ages 19-20. Both cannabis use and cannabis SUD were associated with depression at ages 16-19 and after 25. In adolescents, the association of cannabis SUD and depression symptoms was stronger for females after ages 23-25; however, at ages 19-20, males showed more depressive symptoms (Leadbeater et al., 2019).

SUD+MDD has a higher prevalence of attempted or completed suicide, psychosocial disability, and increased use of healthcare resources, including emergency visits and psychiatric hospitalization (Kaminer et al., 2007). In this line, a follow-up study by Currie et al. (2005) showed that in the last 12 months individuals who experienced MDD and alcohol SUD were at least 20 times more likely to have suicidal ideation, also the life cycle of incidence of SUD+MDD was about 17% compared with 11% in people without SUD. In a study on 307 SUD patients, a relationship was identified between SUD, MDD, and suicide ideas, especially in alcohol SUDs, even in current use or in withdrawal (Pillon et al., 2019). As there are several possible relations between MDD and SUDs, it has been stated that depression may result in earlier SUD and may get worse due to previous substance use. Furthermore, SUD+MDD may increase the risk of dropout, weaker treatment response, and the probability of earlier recurrence (Kaminer et al., 2007). In a study conducted on 517 cancer patients with SUD, it was reported that tobacco use post diagnoses reporters had higher levels of depression compared with alcohol or tobacco non-users. Depressive symptoms were higher between persons with current tobacco use in comparison

to patients who reported past tobacco use and patients who reported no substance use. Nevertheless, they did not find any cause-and-effect relationship between depression and tobacco or alcohol use. Finally, patients with tobacco use post-diagnosis were suffering higher levels of emotions affected by their cancer, such as anger, sadness, fear, or distress in comparison to those who did not use substances (Kosciusko et al., 2019).

Marmorstein (2011) conducted a study on 1,829 participants having a history of MDD episodes. The results indicated that suicidal MDDs were associated with increased risk for all SUDs. Besides, melancholic MDDs were more prone to alcohol use. In a study in the United States on 38 SUD+MDD female prisoners using Hamilton depression scale-17 (HAMD-17), it was reported that the patients had a higher suicide attempt rate (40%) and complex social problems (poverty and sexual victimization) compared to the control group (Johnson & Zlotnick, 2012). Marquez-Aricco et al. (2019b), in a study on 116 males with SUD with and without MDD, observed worse prognosis and treatment outcomes in SUD+MDD compared to SUDs. They reported more comorbidity of medical disorders like hypercholesterolemia, respiratory system diseases, or hepatitis, as well as more antidepressants, anxiolytics, and mood stabilizers. SUD+MDDs showed more use of the substance (e.g. hallucinogens, opioids, and sedatives), more emotional problems, more neuroticism-anxiety, impulsivity, the tendency to being alone, higher difficulty in requesting social support, and more suicide attempts than SUDs. It has been recommended that in adolescents, caffeine use is as a regulator of mood or helper to improve their depression (Owens, 2014). However, as mentioned earlier, the use of substances for regulating the activation and mood increases the problem in medium or long terms. So far, limited research has been done on DD and depression. In Table 4, studies conducted on SUD+MDD patients or SUD patients with depressive symptoms are introduced.

Table 4. Relations among individual characteristics with substance use disorder (SUD) comorbid with major depressive disorder (SUD+ MDD) or SUD with depressive symptoms. A revision of the published works from 2005 to 2020.

Authors	Sample	Measures	Results
Currie et al. (2005)	N = 36984 (SUD+MDD) age not specified	WMH-CIDI CCHS 1.2	The 12-month prevalence of MDD, drug dependence and alcohol dependence have been estimated in persons with SUD. SUD co-occurred with a high frequency in

			cases of MDD. SUD and MDD independently anticipated a higher rate of suicidal thoughts and mental health treatment use.
Johnson & Zlotnick (2012)	N = 38 (SUD+MDD) 35 ± 9.2 yrs.	HAMD-17	MDD+SUD patients had more attempted suicide (40%) and complex social problems (poverty and sexual victimization) than the control group.
Antúnez et al. (2016)	N= 80 (SUD+MDD and SUD) 39.94 ± 9.20 yrs.	SCID-I, DAST-20 HAMD-17 CSM	No differences were seen in years of schooling, the number of substance use, time of abstinence, and SUD onset. SUD+MDD showed more suicidal attempts and more drug consumption than SUD. No difference was observed neither in MT/ET scores nor in CT, sleep-wake schedules, and distal skin temperature.
Adan et al. (2017b)	N = 80 (SUD+MDD and SUD) 40.05 ± 9.29 yrs.	DAST-20, HAMD-17, CSI	SUD+MDD showed a higher percentage of comorbid diseases, suicidal attempts, use of daily medications, and more use of opioid and sedative drugs. SUD+MDD patients displayed a higher use of situation avoidant and lower scores in problem-solving, cognitive restructuring, social support, and self-perceived capacity for coping.
Ahmadi et al. (2018)	N = 51 32.87 ± 7.50 yrs.	BSSI	Groups did not differ in sociodemographic data. Buprenorphine has been considered as an acceptable anti-suicidal anti-depressive in SUD+MDD patients. Although buprenorphine could rapidly treat suicidal ideations and a significant reduction has been reported in suicide scores within each group, no significant difference was observed between groups.
Ihongbe et al. (2018)	N = 9,272 (men: 4398) Age not specified	CESD, MTF	Approximately 8% of high-school seniors reported cannabis use in the last 12 months and 24% reported high depressive symptoms. Generally, cannabis use was not related to depression. About 33% of students reported low levels of depression and 24% reported a high level. Cannabis and illicit drugs were associated with medium and high depression. Cigarette smoking is associated with high and alcohol use is related to low levels of depression.
Mohammad Nia & Mashhadi (2018)	N = 260 (Sex and age not specified)	BDI-S, PMI, IAPS	Negative relationships were reported between depression and the meaning of life, and between the meaning of life and the attitude toward substance abuse. The effect of meaning in life on the relationship between depression and attitude toward the use of substance had been supported.

Kosciusko et al. (2019)	N = 517 (men: 328) 62 ± 10.9 yrs.	CSM, CDC, CES-D, IPQ-R	Reporters of tobacco use post-diagnosis indicated higher levels of depression in comparison with tobacco users or no alcohol or tobacco users. Depressive symptoms were higher between persons with current tobacco use compared to patients who reported past tobacco use and no substance use. Patients with a history of alcohol use reported higher depressive symptoms compared to those who used alcohol post-diagnosis and those who reported no substance use. Patients with tobacco use post-diagnosis were suffering higher levels of emotions affected by their cancer, such as anger, sadness, fear, or distress compared to those who did not use substances.
Leadbeater et al. (2019)	N = 662 adolescent data (men: 320) N = 36,309 adults data (men: 13,761) Age not specified	Mini interview, SCL-90	Cannabis use disorder was related to depression at the age of 19-20 years. In adults, cannabis use was associated with mental health symptoms like depression at most ages (18-61 years). A significant association between cannabis use and cannabis use disorder and depressive symptoms in adults and adolescents spread along adulthood with a mixture of anxiety.
Marquez-Arrico et al. (2019b)	N = 116 only men 40.58 ± 8.03 yrs.	SCID, DAST-20 HAMD-17 ZKPQ	SUD+MDDs were more single and separated than SUDs. Generally, SUD+MDDs reported worse prognosis and treatment outcomes than SUDs. They reported more comorbidity of medical disorders like hypercholesterolemia, respiratory system diseases, or hepatitis, and more antidepressants, anxiolytics, and mood stabilizers. SUD+MDDs showed more use of substances (e.g. hallucinogens, opioids, and sedatives). more emotional disorders, more neuroticism-anxiety and impulsivity, more tendency to be alone, higher difficulty in requesting social support, and more suicide attempts than SUDs.
Pillon et al. (2019)	N = 307 (men: 238) 18-49 yrs.	ASI-6, SADD	Suicide ideas were reported in those with higher depression, anxiety, and those who were under drug use or withdrawal. Cocaine was the first substance use among patients. About 33% of patients reported alcohol SUD. Findings confirm the relationship between depression and suicide ideas. Most of SUD patients reported depression.
Servatyari et al. (2019)	N = 370 (sex not specified) 16-19 yrs.	BDI, Disappointed questionnaire, IAPS	There was a significant relationship between disappointment, economic status, and smoking history in students. Up to 66% of students in this study reported disappointment. Depression and disappointment play a key role in QOL and predict addiction tendency in adolescents.
Zhou et al. (2019)	N = 106,142 (only women) 18-44 yrs.	NSDUH	MDDs and/or anxiety disorder had a higher prevalence of substance use and SUD than those with no major depressive episode or anxiety disorder. A majority of patients with SUD, especially alcohol users, did not receive any treatment. Less than a quarter of patients with SUD, MDD, and anxiety disorder received

			treatment for substance use and mental health. In women with MDD or/and anxiety disorder, the prevalence of tobacco, illicit drug use, and SUD in the past 2-12 months was higher than among women with neither.
Levola et al. (2020)	N = 80 (men: 50) 39.6 ± 13.2 yrs.	ICD-10, SAH, SCQ, , BDI	More severity of MDD was associated with both poorer self-rated health and QOL also more comorbidities than non-MDD ones. There was no significant difference in gender in this regard. More SUD dependence was reported in those with more comorbidities. Back pain, high blood pressure, and liver disease were more observed in reported somatic comorbidities.
Lee et al. (2020)	N = 404 (men: 323) 19-65 yrs.	WHOQOL-BREF	Social support was negatively associated with depression. Social support and depression had a significant mediating effect on the QOL in alcohol SUD. Patients with alcohol SUD with both high QOL and social support reported lower depression. Social support showed a key role in improving alcohol SUD patients.

AUDIT (Alcohol Use Disorders Identification Test); ASI-6 (Addiction Severity Index); AUDIT (Alcohol Use Disorders Identification Test); BDI (Beck Depression Inventory); BSSI (Beck Scale for Suicidal Ideation); CCHS (Canadian Community Health Survey: Mental Health and Well-Being); CDC (Disease Control and Prevention); CESD (Center for Epidemiologic Studies Depression Scale); CSM (Composite Scale of Morningness); CSI (Coping Strategies Inventory); CES-D (Center of Epidemiologic Studies-Depression Scale); DAST-20 (Drug Abuse Screening Test-20); HAMD-17 (Hamilton Depression Rating Scale); IAPS (Addiction Potential Scale); ICD-10 (Classification of Diseases, 10th revision); IPQR (Illness Perception Questionnaire-Revised); MTF (Monitoring the Future); NSDUH (National Surveys on Drug Use and Health); PMI (Personal Meaning Index); SADD (Short Alcohol Dependence Data); SAH (Self-Assessment of one's Health); SCID (Structured Clinical Interview for the DSM-IV); SCL-90 (Symptoms Checklist 90-Revised); SCQ (Self-Administered Comorbidities Questionnaire); WHOQOL-BREF (World Health Organization Quality of Life Scale-Abbreviated Version); WMH-CIDI (World Mental Health Composite International Diagnostic Interview); ZKPQ (Zuckerman-Kuhlman Personality Questionnaire).

1.6. Circadian Rhythms in Substance Use Disorders and Dual disorders

1.6.1. Substance Use Disorder

CRs, especially SPs, have a significant negative impact on physical and mental health, and on cognition and mood. More importantly, they can be closely linked with the use of substances (Adan, 2013). Substances use can disturb sleep at any age, but particularly both sleep problems and drug-seeking behaviors increase during adolescence. SP is one of the most common results of the use of and withdrawal from SUD such that it reported in up to 90% of alcoholics. SUD affects sleep physiology including the neurotransmitter systems that control the sleep-wake-cycle (Conroy & Arnedt, 2014). Individual distinctions in sleep quality and circadian organization may forecast initial vulnerability to drug use and SUD (SAMHSA, 2017). In other words, poor sleep quality increases substance use-related behaviors (Telzer et al., 2013) as nicotine and alcohol (Haraszti et al., 2014b; Roenneberg & Merrow, 2016); however, this relationship is still unclear (Bartel et al., 2016). SUDs show disrupted CR, which may increase the risk of substance use and relapse (Nowakowska-Domagała et al., 2016). Kenney et al. (2012) stated that poorer sleep length was related to greater alcohol use results in heavy drinkers. In contrast, others such as Gottlieb et al. (2006) and Patel et al. (2004) found an association between longer sleep times and an increase in alcohol use. This divergence of results may be due to the stage and characteristics of consumption in the study participants.

Another cause of SPs is co-occurring or comorbidity with other mental disorders, such as the use of substances, medications, and intervention of environmental factors (Brower, 2015). Interaction between SUD and CR changes could turn into a vicious circle by promoting and holding the SUD and their pathophysiological results (Antúnez et al., 2016). The association between substance use and SP is mutual but SP may establish a way for substance use and then self-remedies; hence, adolescents may turn to drugs to increase daytime alertness while to decrease depressive mood and SPs, they prefer to use alcohol and cannabis (Bootzin & Stevens, 2005). In Iran, self-medication, with a high prevalence of nonmedical drugs (53%), can be a spark that ignites the substance use (Azami-Aghdash et al., 2015) as smokers believe that the use of substance neutralizes their fatigue or concentration difficulties (Hamidovic & Wit, 2009). Any self-medication for SPs with drugs can become a vicious cycle in which each of these factors impairs

the other (Bootzin & Stevens, 2005) and may also influence indirectly via correlated emotional disturbance and stress (Hasler et al., 2012a). Therefore, SP is expected to be frequently accompanied by any SUD associated with CD (Hasler et al., 2012a; Pasch et al., 2012; Bartel et al., 2015). In this respect, sleep is disturbed in alcohol SUD patients, and insomnia is reported between 40 and 70% in these patients. In a 1-year follow-up self-reporting study in the United States on 4353 (7-12th-grade) students, insomnia was associated with cigarette smoking, drunk driving, delinquency, and more violence (Shochat et al., 2014). Studies on alcoholic patients have reported that after the treatment, the patients who were most likely to get relapsed had insomnia before remission (Brower et al., 2001; Bootzin & Stevens, 2005).

The relationship between SUD and ET has been revealed in several studies (Prat & Adan, 2011; Hasler et al., 2013). The lower regularity in the CRs has been mostly connected with consumption of legal (alcohol, tobacco, and caffeine) and illegal drugs (cannabis and cocaine) (Adan, 1994; Prat & Adan, 2011; Haraszti et al., 2014b; Vollmer et al., 2014). In all cases, more consumption is detected in ETs compared to MT and IT. Alcohol consumption affects the functions of the circadian clocks (Patron, 2015) and extreme alcohol drinking may disrupt CRs while CR problems may encourage excessive alcohol drink (Logan et al., 2014). A study by Reinberg et al. (2010) has claimed that drinking a glass of red wine during dinner desynchronizes circadian time and decreases night functioning (reaction time) and melatonin secretion. Likewise, another study has reported SP and ET as risk factors for reversion to alcohol abuse and SUD (Hasler et al., 2012a). Also, it has been indicated that accompanying sleep and CD with an increased incidence of ET during adolescence may partially justify the appearance of substance use during this period (Ernst & Fudge, 2009; Hasler et al., 2013). In this sense, ET in adolescence can predict many negative health outcomes and risk behaviors in young adulthood including drug use, emotional distress, thought and social problems, and criminal activity (Urbán et al., 2011; Asarnow et al., 2014).

Smoking, alcohol drinking, caffeine consumption (Baron & Reid, 2014), and a tendency to ET (Conroy & Arnedt, 2014) are some factors that trigger the onset and persistence of substance use. For example, MT seems to be a protection factor, while ET is presently being considered as a risk factor in the beginning and progression of drug consumption (Adan, 2013; Conroy & Arnedt, 2014; Antúnez et al., 2015; Tonetti et al., 2015). Some studies carried out in several countries have confirmed the involvement of extreme CT groups as a protective/risk factor for substances

consumption as well as related risky behaviors that lead to lack of control for use of substances (Prat & Adan, 2011; Lemoine et al., 2013; Kervran et al., 2015; Müller et al., 2016a; Nowakowska-Domagała et al., 2016), especially in alcohol use (Hasler et al., 2015).

In the Iranian population, limited research has been done on CR, CT, and SUD. In relevant studies, the MT group was less inclined to use drugs than to ET (Zargar et al., 2012) and ET was related to more risky behaviors (Ghaseminejad et al. 2015: Merikanto et al., 2017). Besides, it has been reported that the quality of sleep plays a more important role than CT type in the SUD prediction. This hypothesis is reinforced by the fact that the quality of sleep can be considered as a disorder or a problem, as it has been observed in a healthy population. Moreover, ET individuals with a higher likelihood of using substances have more attention problems and decreased daytime functioning compared to those with IT and MT (Abe et al., 2011; Lemoine et al., 2013; Merikanto et al., 2015; Antypa et al., 2016).

Patten et al. (2000) found that in adolescents, smoking, depressive symptoms, female gender, and Asian background were the prognostic factors for the development of SPs. A study with adolescents who referred for SUD treatment also reported problems associated with their sleep such as daytime drowsiness, falling asleep, and nightmares. The use of alcohol to help them sleep in adolescents was 76% of males and 88% of females (Bootzin & Stevens, 2005). In another study, it has been reported that out of those who referred to the treatment of alcohol use, the range of sleep problems was from 25 to 72% (Stein & Friedmann, 2006). Also, withdrawal from cocaine has been reported in three-quarters of people who experienced SPs and low sleep quality (Sofuoglu et al., 2005). These observations, with some differences, will be probably applied to all drugs. For instance, smoking and nicotine consumption involve more sleep fragmentation, sleep onset latency, and decreased sleep efficiency (Jaehne et al., 2009). Arrona-Palacios et al. (2020), in a study on 510 Mexican population to determine the rate of addiction, sleep habits and, CTs, indicated that extreme ET types show more SJL, alcohol, and tobacco use. IT extreme ones showed more oscillation on weekdays and free days. In terms of tobacco consumption, MT men consumed more while ITs used it less than women. In MTs, weak types reported more tobacco, caffeine, and cannabis use than ITs.

The impact of substance use on SQN leads to misalignment among the central clock and rhythmicity (i.e., sleep-wake-cycle, body temperature, melatonin) and the light/dark cycle. For instance, a recent study claims that chronic use of alcohol affects SQN control/activity and leads to CD (Afonso et al., 2014). Falcón et al. (2009) have indicated that the effects of drug addiction on CR can last for weeks or even months after cessation of drug use. Poor sleep quality has been reported as a risk factor in the relapse of cannabis use after 2 days of withdrawal (Babson et al., 2013). Besides, people who reduce marijuana may experience SPs in the first days of withdrawal (Vandrey et al., 2011) and these troubles can continue for weeks (Bolla et al., 2010). A recent study by Bender et al. (2020), carried out on 14 nicotine smokers, reported more sleep disruption, more daytime sleepiness, longer sleep latency, and more arousal. All smokers relapsed after two weeks compared to the control group. After quitting, sleep disturbance problems persisted during the quit attempts but daytime sleepiness remained for a time and may promote the nicotine relapse.

Hasler et al. (2013) demonstrated that the use of substance and CTs plausibly correlate with brain reward function. MT and ET differed in their patterns of brain reactivity to reward during the reward anticipation and win result situations; this dysregulation is linked to substance use. Also, SP by damaging attention and inhibitory method may increase drug use through two mechanisms: 1) rising the worth of drug rewards relative to other rewards or 2) persuading mood states that ease the use of a drug. Hamidovic & Wit (2009) reported that SP increases smoking because smokers believe that it will decrease their sleepiness. Owing to these reward systems, an association between smoking, coffee, and alcohol use among smokers has been observed (Jaehne et al., 2009). Therefore, regular CR especially in sleep-wake problems may help to reduce addiction vulnerability and/or diminish the risk for worsening substance use disorder (Logan et al., 2014).

1.6.2. Schizophrenia

According to estimates, about 16% of the world's mental illnesses are SZ and these patients occupy 50% of the beds of mental hospitals (Abolghasemi, 2007). Irregular sleep in patients with SZ has been depicted since the 1920s (Wulff et al., 2010). Also, the association between SZ and irregular sleep was first explained in the late 19th century by the German psychiatrist Emil Kraepelin (Kraepelin, 1992; Manoach & Stickgold, 2009). SP is represented in 30-80% of patients with SZ (Cohrs, 2008; Lemoine et al., 2013), especially insomnia (Monti et al., 2013). A recent study

estimated that clinical insomnia in the patients with the first episode of psychosis was 22.6% (Subramaniam et al., 2018).

There is a handful of studies that estimate disruptions in CR of SZ patients (Boivin, 2000; Afonso et al., 2014; Robillard et al., 2015). These studies show reduced sleep output and full sleep time, as well as decreased rapid eye movement (REM), sleep latency (Bromundt et al., 2011, D'Agostino et al., 2018), and slow-wave sleep duration (Monti et al., 2013). Several sleep factors such as sleep period (the space between sleep onset and termination) and total sleep time are longer in SZ patients than healthy controls (Tam et al., 2015). SP has also been recognized as a threat factor in the manifestation of psychosis in young people at the risk of SZ (Wilson & Argyropoulos, 2012). Poor sleep quality is linked to a low QOL in these patients (Klingaman et al., 2015; Subramaniam et al., 2018) and often reduced quality of sleep and sleep time go untreated in these patients (Kaskie et al., 2017). Sleep variations play an important role in the neurophysiological (Jagannath et al., 2013; Onitsuka et al., 2013) and cognitive impairments (Riedner et al., 2011) such as deficits in working memory and attention, problem-solving, processing speed, social cognition (Sachs et al., 2007), verbal memory, executive functioning, and vigilance (Bromundt et al., 2011) in SZ patients. Cognitive impairments in younger SZs are considered more severe compared with bipolar/depressive disorders (Keefe, 2008) and cognitive improvement in people with SZ is contingent on improving sleep parameters (Wilson & Argyropoulos, 2012).

SPs can act as a predictor of next-day reduced functioning and impaired psychotic symptom severity in SZs (Mulligan et al., 2016). In a comparison study of rest-activity of SZ patients with a healthy control group, a significant SP or CD was reported in all patients with SZ, and problems in melatonin secretion were observed in half of them compared to the healthy group (Wulff et al., 2012). In terms of CT, in an epidemiological study of the 2-year period (2005-2007) among 1468 patients including several mental disorders, it was observed that the patients with psychosis were more likely to be MT (Lemoine et al., 2013). Thomas et al. (2018) in a study on 320 participants, including mood disorders, SZ, other relative patients with SZ and health group, showed that SZs were likely to be ET. SZ patients often show irregular sleep-wake patterns. Besides, it has been evidenced that the sleep and CR disturbance are associated with the intensity of positive, negative, and cognitive symptoms of SZ (Pritchet et al., 2012; Tam et al., 2015). A study by Chung et al. (2018) in 66 SZ patients showed that higher irregularity sleep time was significantly associated

with late consumption of caffeine, higher PSQI scores, greater social rhythm irregularity, later dinner times, and greater severity of positive symptoms. So, it not surprising why SP in SZs has significant negative effects on the performance and modality of life of these patients (Bromundt et al., 2011; Pritchet et al., 2012).

Continuous insomnia can lead to a reversal of the diurnal rhythm in patients with SZ. Thus, it leads to extreme daytime drowsiness with a propensity to sleep during the day and stay awake at night (Afonso et al., 2014). Therefore, the link between insomnia and SZ is bidirectional. SZ exacerbates sleep disturbances, while insomnia can worsen the SZ symptoms (Cosgrave et al., 2018) and even it may further increase the risk of suicide in these patients (Li et al., 2016). Consequently, SZ patients withdraw both social lifetimes and daylight, leading to further problems in CRs (Bromundt et al., 2011). These changed sleep patterns may strengthen worries with the social occupation, and depressive symptoms related to SZ (Afonso et al., 2014). Researchers have argued that reduction in stage four of sleep is the steadiest and clinically significant observation in chronic SZ (Caldwell, 1969; Hiatt et al., 1985; Boivin, 2000).

Problems in the circadian system can lead to CD, which itself leads to SPs, reduced attention and daytime alertness, absence of energy, memory troubles, and negative mood in individuals with SZ (Foster et al., 2013). Up to 80% of patients with severe mental illness such as SZ report sleep irregularities that influence physical and mental health (Monti et al., 2013).

SPs often occur before the onset of psychotic symptoms in vulnerable people to psychos and can predict an acute relapse in chronic and improved SZ (Kahn-Greene et al., 2007), as far as SPs can lead to psychotic features such as perceptual changes and paranoia. It has been reported that moderate or severe insomnia was obvious in 54% of the SZs with persecutory delusions compared to 7.4% of the community sample (Freeman et al., 2009). Having longer sleep latency leads to increase waking after sleep onset as well as reduced sleep efficiency in chronic SZ patients (Yang & Winkelman, 2006). It has been reported that psychosocial stress, psychotic symptoms (Lim et al., 2009; Afonso et al., 2011), negative symptoms, cognitive deficits (Waite et al., 2016), substance-induced insomnia, and high rate of SUD (Volkow, 2009) can cause sleep disturbances and even high prevalence of insomnia in SZ patients.

Foster (2013) concentrating on adolescents at the risk of developing psychosis, without mania, or depressive symptoms reported that 37% scored high on SPs and adolescent girls gained higher scores than adolescent boys. Also, a great range of breathing sleep-disordered was discovered among SZ patients, as more respiratory disturbance especially in men (Winkelman, 2001; Naqvi et al., 2014; Klingaman et al., 2015). A recent study conducted on 1,230 participants including SZ patients, BD patients, and healthy control groups revealed that the most sleep disturbance among three groups belonged to SZ patients, which is about 80%. Sleep disturbances of SZ patients were attributed to more depressive, negative symptoms, and lower functioning (Laskemoen et al., 2019).

Thalamus as a structure for sleep regulation is steadily reduced mutually among SZs (Byne et al., 2009). So, thalamic abnormalities are just one recommended neurobiological mechanism that clarifies the connection between SZ and insomnia (Bennett et al., 2009). Another recommended mechanism for this connection includes dopamine dysregulation in SZs, especially the dopaminergic D2 receptor (Monti et al., 2013). Hence, treatment for sleep disorders for SZ patients is especially essential when observing a high frequency of sleep problems (Wulff et al., 2010; Lemoine et al., 2013; Klingaman et al., 2015). Although sleep and CR disturbance is infrequently aimed for treatment of SZ, when it is the case, patients announce developments in both their sleep quality and psychiatric symptoms (Pritchet et al., 2012) such as negative symptoms (Chiu et al., 2016). To the best of our knowledge, limited research has been done on CR in SZ, SUD, and SUD+SZ patients so far. Table 5 summarizes the conducted studies during 2011-2020 in these 3 groups of patients.

Table 5. Relations among circadian rhythms and individual characteristics with substance use disorders (SUD), schizophrenia (SZ) and their comorbidity (SUD+SZ). a revision of the works published from 2011 to 2020.

Authors	Sample	Measures	Main Results
Bromundt et al. (2011)	N = 14 (men13) (SUD+SZ) 39.9 ± 9.6 yrs.	PSQI	Sleep-wake-cycles in individuals with SZ ranged from well-entrained to highly-disturbed rhythms.
Hasler et al. (2013)	N = 310 (men:310) 20 yrs.	CSM, Barratt Impulsiveness Scale-11, PSQI,	ETs reported greater degrees of dysregulation on all clinical measures, higher frequencies of SUD, and more severe symptoms of alcohol dependence.

			ETs showed worse objective and subjective sleep quality, and longer sleep latency.
Ghaseminejad et al. (2015)	N = 150 Age not specified	CSM, PSQI, Iranian Addiction Potential Scale, ASI	MTs had less tendency to use substances, and ETs were more prone to SUD. Individuals with low quality of sleep had more tendency to use substances. Quality of sleep predicted addiction more than CT type.
Kervran et al. (2015)	N = 333 (men: 209) (SUD+SZ) 39.8 ± 11.4 yrs.	MEQ, MINI, ASI,	ET was associated with more problematic addiction, more cannabis use, mood problems, and polydrug use. MT was related to antisocial personality disorder.
Tavernier et al. (2015)	N = 942 (men: 269) 19.0 ± 0.90 yrs.	ISI, SACQ	The majority of participants were ET. ET was significantly associated with poorer academic adjustment, higher SUD, more SPs, and higher SJL. SUD was a significant predictor of higher SJL.
Nowakowska-Domagała et al. (2016)	N = 85 (men: 85) (SUD & personality) SUD = 47.66 ± 10.22 Control group= 46.36 ± 10.4	CHQ, EPQ-R, MAST,	Alcohol-dependent men were more neurotic than the control group. Higher neuroticism was related to both extreme ET and MT. MT was found in most of the alcohol-dependent patients and in the control group. The mostly observed CT (41%) was IT.
Capella et al. (2018)	N = 114 (SUD) 35.26 ± 0.71 yrs. (healthy control) N = 103 37.68 ± 1.11 yrs.	CGI, DAST-20, GSS, CSM,	More MT was observed in the SUD group. Distal skin temperature indicated that the SUD patients presented globally a better circadian functioning (lower minimum temperature and circadian index) in contrast to the healthy control group.
Chung et al. (2018)	N = 66 (men: 30) 44.08 ± 12.64 yrs.	CSM, PSQI, PANSS, BMI, VFT, SOFAS,	A higher rate of irregularity timing in bed was related to later caffeine use, higher PSQI scores, and more social irregularity rhythm. Higher abnormality in sleep efficiency was related to later dinner time and lower hypnotic daily dose. Problems in waking up after sleep onset were associated with lower antipsychotic dosage.
Laskemoen et al. (2019)	N = 1230 (men: 655) SZ = 617 BD = 440 Healthy control: 173	SCID, PANSS, GAF-F- IDS-C	Sleep disturbance in SZ was around 80% and more than BD and healthy control. Insomnia and sleep disturbances were more frequent both in SZs and BDs than healthy ones. Sleep disturbance was related to more depressive, negative symptoms, and lower functioning in SZ patients. SZs were younger, more male gender, had a lower level of education, reported more drug dependency, hypersomnia, delayed sleep phase, and antipsychotic medication, and showed fewer mood stabilizers than bipolar ones.

Arrona-Palacios et al. (2020)	N = 510 (men; 282) 27.79 ± 10.24 yrs.	MESSI	ET extreme types reported more SJL. Clearly, IT extreme types showed more amplitude on free days and weekdays. ETs consumed more alcohol and tobacco. In MTs, men reported more use of tobacco days/week than women. In comparison, IT women showed more use of tobacco but men reported more use of caffeine. Women consumed more alcohol compared to men in more days of the week. Also, MTs weak types reported more tobacco, caffeine, and cannabis use than ITs.
Bender et al. (2020)	N = 28 Sex not specified 27.6 ± 5.6 yrs.	FTND, PST, KSS, PSQI	Smokers reported more sleep disturbance before and during the quit attempt. Smokers showed more daytime sleepiness. All smokers relapsed after two weeks. After quitting, daytime sleepiness still remained.

ASI (Addiction Severity Index); BMI (Body Mass Index); CHQ (Ogińska's Chronotype Questionnaire); CGI (Clinical Global Impression Questionnaire); CSM (Composite Scale of Morningness); DAST-20 (Drug Abuse Screening Test-20); EPQ-R (Eysenck's Personality Questionnaire-Revised); FTND (Fagerström Test for Nicotine Dependence); GSS (Global Seasonality Score); GAF-F (Scale-Split version-function score); ISI (Insomnia Severity Index); KSS (Karolinska Sleepiness Scale); IDS-C (Depressive Symptoms Clinician rated scale); MAST (Selzer's Michigan Alcoholism Screening Test); MESSI (Morningness-Eveningness-Stability-Scale-Improved); MEQ (Morningness-Eveningness Questionnaire); M I N I (Mini International Neuropsychiatric Interview); PANSS (Positive and Negative Symptom Scale); PSG (polysomnography); PSQI (Pittsburgh sleep quality index); PST (Positive Symptom Total); SCID (Structured Clinical Interview for DSM); SCL-90 (Symptom Checklist-90-R); SACQ (Student Adaptation to College Questionnaire); SOFAS (Social and Occupational Function Assessment Scale); VFT (Verbal Fluency Test).

1.6.3. Major Depressive Disorder

MDD is the world's most usual psychiatric disease (Soria et al., 2010) and according to the WHO, MDD was the first universal cause of disability and is viewed as a major problem affecting more than 350 million people around the world (Schnell et al., 2014) with rate of which in Western countries near 10% (Morita et al., 2015). Genetically, 37% of MDD is determined by heredity (McCarthy & Welsh, 2012). One of the first circadian assumptions for MDD is that depressed persons sleep at a significantly later circadian phase compared to healthy individuals. This circadian misalignment in the patients with MDD has been connected to an irregular daily form of gene expression, hormonal secretion, body temperature, and cognitive/behavioral functions (Levandovski et al., 2011). Early in the morning, the body temperature goes up and gradually ascends to the evening, and then begins to go down (Bunney & Potkin, 2008). MDD patients have higher nocturnal and 24 h overall mean core body temperature (Rausch et al., 2003). In this regard, remission of symptoms is associated with normalized temperature rhythms (Lam, 2006; Lewy et al., 2006; Bunney & Potkin, 2008). Normal hormonal secretion of melatonin rises before bedtime, remains high during nighttime sleep, but decreases rapidly during the waking time and secretion is minimal during the daytime period (Zeitzer et al., 2000). Thus, about 2 hours before sleep, the melatonin hormone secretes in low light conditions. In depressed people, this process has a delay suggesting a phase delay in the circadian rhythms of these patients (Levi, 2007). Serretti et al. (2003) reported that polymorphisms in clock protein (homozygous for the C alleles) are relevant to sleep abnormalities in MDD patients.

Reports approximate that 50-90% of MDD patients complain about impairment of sleep modality (Monteleone & Maj, 2008; Gaspar-Barba et al., 2009). Patients who suffer from a depressive episode report changes in their sleep index (Wulff et al., 2010), especially complaining about insomnia (Müller et al., 2016a), poor quality of sleep, and SPs (Dallaspezia & Benedetti, 2011). Depression and insomnia have been reported higher in women than in men at any age (Morita et al., 2015). Electroencephalographic (EEG) of sleep in depressed patients suggests a dysfunction in sleep parameters including a faster onset of REM sleep and a decline in slow-wave sleep (Lam, 2006). A longitudinal study on 7,900 participants has depicted that insomnia is a risk factor for the development of depression (Monteleone & Maj, 2008), and irregularity of sleep might be a risk factor for depression (Bootzin & Stevens, 2005; Kronfeld & Einat, 2012; Morita et al., 2015;

Tochigi et al., 2016). For instance, up to 80% of individuals with MDD have disruptions in their sleep and poor sleep quality anticipates the beginning of MDD (Gobin et al., 2015). Moreover, MDD causes trouble in starting and keeping sleep during the night. Continuous insomnia increases the risk of recurrence into a new MDD episode (Wulff et al., 2010). In young adults, insomnia was a risk factor for later depression persisting for at least 30 years and increased the risk of relapse after an MDD episode (Monteleone & Maj, 2008). The National Institute of Mental Health Epidemiologic Catchment Area (MHECA) studied a total of 7,954 adults and emphasized the robust association between sleep problems and subsequent depression. It also found that 14% of patients with insomnia had developed a new MDD episode one year later (Wilson et al., 2010). Thus, the prevalence of depressive symptoms between the patients seeking treatment for insomnia is high (nearly 63%) (Bei et al., 2015).

In an interview on the relations between insomnia, depression, and anxiety among more than 1,000 adolescents aged 13-16 years old, it was realized that insomnia increases the risk for depression (Shochat et al., 2014). Reviewing the sleep-wake-cycle and 24-hour activity profiles of 238 bipolar/depressive patients showed the effects of younger age on higher depression severity and the sleep-wake-cycle, but not on sleep duration (Robillard et al., 2014). Popular primary theories combining sleep and CRs to mood episodes have shown that in bipolar/depressive disorders including the sleep-wake-cycle, the endogenous circadian pacemaker becomes misaligned. Therefore, the recording of SP serves as a psychobiological marker of bipolar/depressive disorders (Asarnow et al., 2014) around 30-60% (Steinan et al., 2016). Besides, mood alterations were following the circadian time and associated with several other measures of CR (Bechtel, 2015; Hwang et al., 2016). For example, seasonal variations in mood, behavior, and social activity were related to dysregulation of the circadian system in the people with BD (Bullock et al., 2014).

More than three decades of investigation have provided convincing evidence of CR abnormalities in bipolar/depressive disorders (Hasler et al., 2009; Jagannath et al., 2013; Pilz et al., 2018). Depressed individuals may endure abnormalities in CR caused by stressful life occurrences (Friborg et al., 2014). A recent study suggests that CR misalignments are associated with higher risks for future psychiatric disorders (Pilz et al., 2018). The work undertaken by Merikanto et al. (2013) showed that in addition to the increased resting heart, antidepressant medication had high frequency among ETs. The patients with MDD have reported both shorter and longer sleep

durations, trouble in falling asleep (Bron et al., 2016), and more proclivity to ET (Hasler et al., 2015). A recent longitudinal study in the Netherland reported that ET did not predict a persistent depressive period and suggested that CT might be an unstable predictive factor in clinical features (Druiven et al., 2019) and could the reason that the stability of CT can change by variations in MDD severity (Druiven et al., 2020).

Variation of the sleep-wake phase and sleep structure is present during the disorder and fundamental indicators of an MDD episode (Boivin, 2000, Luik et al., 2015; Druiven et al., 2020). However, the physiological and biological mechanism links that elucidate the association between CRs and mental problems, especially in bipolar/depressive disorders, are unclear (Wulff et al., 2010; Li, 2013; Miller et al., 2015; Togo et al., 2017). Available data suggest distinct connections between CR disruption, SPs, and bipolar/depressive episodes (McClung, 2007; Levandovski et al., 2011; Hickie et al., 2013; Alvaro et al., 2014; Kervran et al., 2015). Nonetheless, the mentioned connections may be due to the impact of the molecular clock on neurotransmitters systems and their receptors (McClung, 2007). ETs may be less exposed to the light, which can worsen their depression (Lester, 2015). Other possible mentioned reasons that expose ETs to more prone to MDD are the specific pattern of thinking in the evening hours (like rumination) (Takano & Tanno, 2011; Antypa et al., 2017) or a type of personality traits that they carry such as dysfunctional impulsivity or novelty-seeking (Adan et al., 2010a,b). In this regard, rumination as a cognitive phenomenon in depressive disorders that often occurs in people a tendency to think deeply at the end of the day (Takano & Tanno, 2011) is long enough to cause depression (Lovato & Geradisar, 2014).

Genetic variants play an important role in the fluctuation of mood, which increases the sensitivity to the environment. As a result, these environmental stressors stimulate pathological fluctuations in mood, which later fluctuates independently, even in case of lack of these stressors (McCarthy & Welsh, 2012). Johansson (2003) suggested that a genetic (gene polymorphisms) basis may exist for the relationship between CT (especially ET) and mood. A comparison of ET and MT insomniacs showed that the ET group exhibited reduced metabolism in the brain, including the medial prefrontal cortex and the striatum (Hasler et al., 2012b). In this case, bipolar/depressive disorders are particularly affected by reduces activities of the hippocampus (McClung, 2007;

McCarthy & Welsh, 2012). Neural imaging has revealed that ETs suffer from atrophy in the subiculum region of the right hippocampus and its connections (Horne & Norbury, 2018a; b).

In healthy humans, the mood is modulated by the circadian phase (McCarthy & Welsh, 2012; Oliveira et al., 2020), and alterations in the circadian system, including the lack of sleep because of travel or overwork, have adverse outcomes on mood, causing irritability and emotional lability (Zanini et al., 2015). In several studies, it has been illustrated that the problems in CR may trigger the pathology of bipolar/depressive disorders, and this abnormal CR often happens in depressive disorders (Schnell et al., 2014; Jeong et al., 2015). For instance, Roberts & Duong (2014) found a mutual association between sleep duration and MDD such that adolescents with shorter sleep had an increased probability of MDD. Recently, a study on 124 patients of alcohol dependence with and without bipolar/depression disorders investigated sleep regulatory index (a novel measure that assesses the probability that an individual is awake) on different races of people including black African American, white, Asian, American Indian, and other ones (Brooks et al., 2020). They found that the average sleep regulatory index in persons without bipolar/depression disorder is higher than those with the disorders. Sleep regulatory scores were associated with a lower total nap and decreased mental/physical exhaustion scores from the first week until the third week. Finally, despite an association between lower quality of sleep scores and higher regular sleep, they did not report any significant relation between the total sleep regulatory index and sleep quality scores. Therefore, misalignment in CR may be a part or result of the developing mental disorders such as MDD (Ross et al., 2016) or maybe a concomitant risk factor associated with sexual growth (Jagannath et al., 2013).

It has been determined that the type of CT can change by variations in depression severity (Druiven et al., 2020), and poor sleep quality may mediate this association (Selvi et al., 2018). Available data show the significant association between depressive symptoms and ET (Chelminski et al., 1999; Hidalgo et al. 2009; Zanini et al., 2015; Tonon et al., 2020). In this regard, in a recent study on MDD patients, it was observed that those with good sleep quality reported the lowest depressive symptoms with more tendency to MT than ET and IT (Selvi et al., 2018). In this study, patients with poor habitual sleep quality reported less prior suicide attempts. Furthermore, more sleep latency, more sleep duration, higher use of sleep medication, and more daytime dysfunction were reported in ETs. A study on Spanish and Brazilian people in mood rhythmicity showed that ones

with higher anxiety, pessimism, and sadness have a greater predisposition to psychiatric disorders such as MDD (Pilz et al., 2018). Moreover, it has been reported that the co-occurrence of anxiety, poor sleep quality, and ET tendency increases the probability of more depression severity (Tonon et al., 2020).

Studies have shown that the propensity toward depression increases when work time is not compatible with diurnal sleep (Di Milia et al., 2005; Foster et al., 2013). Moreover, ET depressed patients were more affected in terms of work and activities and revealed greater paranoid symptoms compared to MT and IT (Gaspa-Barba et al., 2009). Kim et al. (2010) studied the relationship between depressive symptoms in 361 healthy participants. The results showed that ET was more obvious in the younger (≤20 years) and older (≥50 years) subjects, compared to the middle-aged group (30-40 years). Multiple studies on high school colleges and medical school students, as well as the general adult people, confirmed a positive link between ET and depressive symptoms (Chelminski et al., 1999; Hirata et al., 2007; Kim et al., 2010; Kitamura et al., 2010; Merikanto et al., 2013). Some studies reported contradictory results between CTs and bipolar/depressive or depression disorders. For example, Müller et al. (2015) found that MTs were significantly less frequent in patients with MDD. Also, they did not find any relation between ET scores and clinical characteristics of MDD patients. In this regard, Sheaves et al. (2016) found weak associations between MT-ET scores and both depression and (hypo) mania symptomatology in 1403 students. Mokros et al. (2017), in a study on 140 students, reported no significant relationship between bipolar/depressive disorders and CT. Finally, in another study, BD patients reported stronger tendencies to MT than ETs and ITs (Wulff et al., 2010).

ET seems to be associated with mood changes (Müller et al., 2016b) and more irregular lifestyles (Jeong et al., 2015). According to zeitgeber theory, it has been suggested that in individuals susceptible to depression, social stress can disturb CRs and lead to depression (Bechtel, 2015). Social rhythms are less steady in MDD patients. It is worth mentioning that social rhythm regularity is negatively correlated with depression scores. In this sense, an increase in MT tendency was correlated with agomelatine response, an antidepressant drug with chronobiological effect, and remission in MDD symptoms (Corruble et al., 2014). Insomnia and MDD are associated with low light exposure. Even reduced physical movement and unstable social rhythms also play a role in sleep and circadian interruptions in depressive disorders (Asarnow et al., 2014). An irregular

lifestyle and a decrease in daily light exposure contact influence the biological clock and mood of individuals and increase the possibility of developing an MDD (Jankowski, 2014; Antypa et al., 2017). A 5-fold increase has been reported in depressive symptoms of healthy individuals ET (Berdynaj et al., 2016); however, 'typical' or 'melancholic' forms were reported more associated with MT. The melancholic form is typically related to decreased appetite and weight loss. In contrast, 'atypical' form is correlated with later sleep onset and offset, overeating, weight gain, and increased risk of metabolic dysfunction (Hickie et al., 2013).

Irregular CTs, reduced REM latency, and early morning awakening are correlated with depression (Bunney & Bunney, 2000). Variations in the CR, body temperature, and hormone secretion occur in MDD patients (Germain & Kupfer, 2008; Malhi & Kuiper, 2013). In other words, the common clinical symptoms of depression are circadian fluctuation (e.g. mood variations and SPs) (Gaspa-Barba et al., 2009), suffering from irregular biological patterns observed in circadian markers of body temperature, melatonin, and cortisol (Grandin et al., 2006). Data showed cortisol awakening response declined in ET of MDD patients (Jankowski, 2016) and even in the severity of depressive symptoms (Tonon et al., 2020). The biological mechanism can act as genetic support in the link between CR and depressive symptoms (Jankowski, 2016). Therefore, it can be claimed that MDD is a candidate disorder as the symptoms are concomitant with defects of the circadian period (Bunney & Bunney, 2000).

Phelps (2004) documented that sleep loss interrupts the programming and later preservation for positive emotional memory. So, insufficiencies in emotion regulation and cognitive processing have been recognized in individuals with bipolar/depressive disorders. Moreover, interrupting sleep indicators has been linked with future manic and depressive symptoms. Undeniably, lower activity levels that are hallmarks of the bipolar/depressive disorders are postulated as suppliers to SP (Asarnow et al., 2014). However, Boivin (2000) did not find any constant relation between mood variability and the severity of the MDD or between the severity of depression and the response to SP. Monteleone & Maj (2008) suggested that MDD patients can recover from their depression by successfully handling their insomnia. Kervan (2015) proposes a robust relationship between depression and ET and supports the notion that ET may be associated with bipolar/depressive disorders. Merikanto et al. (2013) reported that ET individuals were 3.8 times more likely to report depression and anhedonia feeling, more diagnosis of MDD, and were almost

three times more likely to describe the consumption of prescribed antidepressant medication. Recently, in a longitudinal study between 255 youth (11-19 years old) over a 48-month period, it has been highlighted that the participants with earlier depression symptoms and history of depression showed more ET than MT. Moreover, in this study, ET tendency increased in depression symptoms and onset of depression one year later. Finally, the experienced earlier depression in life predicted more tendency toward ET, especially among post-pubertal youth (Haraden et al., 2017). The results of studies about CR and depression are shown in Table 6.

Table 6. The main results of the studies relating circadian rhythms in major depressive disorder (MDD) and/or depressive symptoms. Revision of the works published from 2009 to 2020.

Authors	Sample	Measures	Main Results
Gaspar-Barba et al. (2009)	N = 100 (men:21) 34 ± 11.74 yrs.	HAMD-17 MEQ	ET group indicated higher scores in suicidal thoughts, more impaired work, and activities, and higher paranoid symptoms. MT group showed a lower proportion of melancholic symptoms. No association was found between sleep parameters and specific CTs.
Hasler et al. (2010)	N = 208 19-23 yrs.	Beck Depression,, Inventory, MEQ	ET was significantly associated with higher depression scores.
Abe et al. (2011)	N = 90 (men:54) 27.1 ± 9.2 yrs.	SDS MEQ	Sleep disturbance, fatigue, and psychomotor retardation were the main depressive symptoms. There was a high prevalence of depressive symptoms among the delayed sleep phase syndrome patients. Moderate to severe depressive symptoms were significantly related to ET moderately and ET severely.
Alvaro et al. (2014)	N = 318 (men: 164) 14.97 ± 1.34 yrs.	CSM , CDI , SSHS ,ISI , MESC, RCADS	CT was a risk factor for insomnia and depression. Insomnia predicted depression and panic disorder and was predicted by depression and generalized anxiety disorder.
Bahk et al. (2014)	N = 120 (men: 22) 18-74 yrs.	MEQ HAMD-17, BSI, BIS,	ET group and biological rhythm dysfunction showed higher suicidal ideation. Also, suicidal ideation was positively correlated with ETs and hypomanic personality traits. Suicidal ideation was positively correlated with the severity of depressive symptoms, ET propensities, and hypomanic personality traits. Moreover, ET can be a risk factor of suicide in patients with MDD.
Chan et al. (2014)	N = 253 (men:44) 50.8 ± 10.2 yrs.	MEQ ISI	ET subjects had a more delayed bedtime and wake-time associated with more severe depressive

		GSQ HAMD-17	symptoms, anxiety symptoms, insomnia, more dysfunctional sleep beliefs, higher prevalence of smoking, a nearly significantly higher percentage of alcohol use, and a higher degree of neuroticism and impulsivity.
Corruble et al. (2014)	N = 721 47.5 ± 11.9 yrs.	CSM	ETs were younger and had less regular social rhythms. Depression remitters showed a higher frequency of morning type. MT at baseline is an independent predictor of response to MDD treatment.
De Souza & Hidalgo (2014)	N = 351 (men: 104) 14.70 ± 1.86 yrs.	MCTQ BDI	Sleep phase delay was correlated with higher levels of depression and ET young girls had more possibilities of exhibiting depression. SJL hours were more linked with older age. A significant association was obtained between depression and lateness. Also, sleep on free days and SJL were forecasters of depression.
Bielen et al. (2015)	N =100 MDD: 60 Control: 40 Age not specified	MEQ	In the MDD group, 35% were MT, 58.3% IT, and 6.7% ET. In the control group, 46% were MT, 48% IT, and 6% ET. MDDs were reluctant to do the selected morning tasks completely. Also, they found that depression may be considered as the result or cause of CD.
Borisenkov et al. (2015)	N = 3435 (Men:1517) 14.8 ± 2.6 yrs.	MCTQ	Seasonal affective disorder (SAD) with winter depression affects several sleep characteristics (shorter mean sleep duration and lower sleep efficiency), and it is more obvious on school days. There are significant distinctions in sleep characteristics and CT between people with winter depression and without winter depression. The results showed that in young inhabitants of northern latitudes, both residence and location within the time zone are predictors of winter depression.
Morita et al. (2015)	N = 2502 (men: 1144) 23.0 ± 1.8 yrs.	CESD	Depression and insomnia were more frequent in women than in men. The delayed sleep-wake schedule was more common in men than in women. Moreover, when women had a delayed sleep-wake schedule, they were more vulnerable to develop depression.
Robillard et al. (2015)	MDD: 135 20.0 ± 4.4 yrs. Bipolar: 80 23.1 ± 5.3 yrs. Psychosis: 30 22.5 ± 5.1 yrs. Control group: 41 25.3 ± 5.8 yrs.	Actigraphy monitoring	The number of subjects with a delayed sleep onset was significantly higher in the depression group. Total sleep time was significantly longer in the psychosis group than the control. Psychosis and BD groups had the most variable sleep. All patients had a delayed sleep-wake profile timing.

Müller et al. (2016a)	N = 64 (men: 25) 41 ± 13 yrs.	BDI PSQI MEQ	ET and poor sleep quality were independently and directly associated with higher MDD. ETs had more depression. Cognitive symptoms were more pronounced in ETs. No significant differences were observed in terms of somatic and affective symptoms between ETs and MTs. In sum, CT should be considered in the diagnosis and treatment of depressive disorders.
Antypa et al. (2017)	N = 1654 Depression history: 1227 Control group: 427	CIDI 1, MCTQ, MSF, LEIDS-R, PSWQ, AUDIT	ET is associated with higher cognitive reactivity scores (a specific psychological factor of depression vulnerability), especially in rumination. ET was not an outcome of current depression, but probably a risk factor for increased depressive cognitions and finally depression.
Haraden et al. (2017)	N = 255 (men: 145) 15.03 ± 2.31 yrs.	CDI, K-SADS-PL, MESC, PDS	Youth with higher earlier depression symptoms and a history of depression showed a higher ET. More ET predicted increases in depression symptoms and onset of depression in one year. Experience of earlier depression in life predicts a greater preference for ET.
Tonon et al. (2020)	N = 236 All 18 yrs.	PSQI, MEQ, PSS, SRM,	Individuals with higher stress, ET, poor sleepers reported more depression. Sleep quality and sleep disturbances were reported more in depressed ones. A low level of cortisol in the morning was related to depression.
Brooks et al. (2020)	N = 124 (men; 82) 46.3 ± 9.3 yrs.	PSQI, ESS, Actigraphy, SCID, CIWA-Ar, CPRS, PACS, TLFB	The average of sleep regulatory index for non-bipolar/depressive disorder individuals was higher than persons with one or more bipolar/depressive disorders. Higher sleep regulatory index scores were related to lower total nap, lower mental/physical exhaustion scores during the first and third weeks. Sleep regulatory index and sleep quality were not related, but a negative association between sleep quality and QOL was observed.

AUDIT (Alcohol Use Disorders Identification Test); ASI (Anxiety Sensitivity Index); AUDIT (Alcohol Use Disorder Identification Test); BDI (Beck Depression Inventory); BIS/BAS (Behavioral Inhibition and Behavioral Activation Scales); BSI (Beck scale for Suicidal Ideation); CDI (Children's Depression Inventory); CIDI (Composite International Diagnostic Interview); CESD (Center for Epidemiologic Studies Depression Scale); CIWA-Ar (Clinical Institute Withdrawal Assessment); CPRS (Comprehensive Pathological Rating Scale (CPRS); CSM (Composite Scale of Morningness); ESS (Epworth Sleepiness Scale); GSQ (General Sleep Questionnaire); HAMD-17 (Hamilton Rating Scale for Depression); ISI (Insomnia Severity Index); K SADS PL (Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime Version); LEIDS R (Leiden Index of Depression Sensitivity); MCTQ (Munich Chronotype Questionnaire); MESC (The Morningness-Eveningness Scale for Children); MEQ (Morningness-Eveningness Questionnaire); MSF (Mid Sleep on Free Days); PACS (Penn Alcohol Craving Scale); PDS (Pubertal Development Scale); PSS (Perceived Stress Scale); PSWQ (Penn State Worry Questionnaire); RCADS (Revised Child Anxiety Depression Scale); SCID (Structured Clinical Interview for DSM-IV Axis I Disorders); SSHS (School Sleep Habits Survey); SDS (Self- Rating Depression Scale); SRM (Social Rhythm Metrics); TLFB (TimeLine Follow Back).

2. PROBLEM STATEMENT, OBJECTIVES AND HYPOTHESIS

2.1. Problem Statement

In the last few years, there has been a growing interest in sleep perturbations (Malhi & Kuiper, 2013) such that a great body of studies has focused on the relationship between mood, behavior, and CRs (Ozdemir et al., 2015). As mentioned before, evidence suggests that sleep, CR, and sleep-wake as the main expression of CR are often disturbed in psychiatric disorders (Park et al., 2015). In other words, CR including sleep problems is a risk factor for developing psychiatric perturbations (Malhi & Kuiper, 2013; Fares et al., 2015; Robertson et al., 2019), especially for SUDs and bipolar/depressive disorders (Bootzin & Stevens, 2005). The influence of sleep and CDs is a key factor for future investigations on the development of psychiatric disorders (Asarnow et al., 2014) because both CR and SPs were most often observed during the prodromal phase or earlier to psychotic relapse and bipolar/depressive disorders (Monti et al., 2013).

SPs have an undeniable effect on mental and cognitive functions, somatic indications, social tasks such as road accidents (Bootzin & Stevens, 2005; Wilson et al., 2010; Bartel et al., 2016), and SUD like alcohol (Wulff et al., 2010, Brooks & Canal, 2013; Jagannath et al., 2013). Furthermore, insomnia and SUD promote the risk of one another (Liu & Chung, 2015). Plenty of adolescents with substance consumption also have depression symptoms. Since the concomitant prevalence of SUD and MDD in adults is around 11-27% (Antúnez et al., 2016; Marquez-Arrico et al., 2019b), SPs are considered as a target having a twofold advantage for a successful treatment for both disorders (Bootzin & Stevens, 2005). On this point, findings have shown that improvement of sleep patterns may have a great effect on the treatment of depression symptoms (Tochigi et al., 2016). Moreover, it has been found that sanitation in sleep is related to amelioration in depression symptoms (Dewald-Kaufmann et al., 2014) and SUD withdrawal (Bootzin et al., 2003; Brower, 2015). Thus, an important question raises to be taken into account in the therapeutic management of the patients with these mental disorders alone or comorbid.

Also, three factors with higher disturbance including worse QOL, higher risk of suicide (Antúnez et al., 2016), and disturbances in sleep and CR (Kervran et al., 2015) in several mental disorders have made a strong impetus for us to exert more investigations about the SUD, SUD+MDD, and

SUD+SZ disorders. There is an amplified risk of later MDD in primary insomnia (Wilson et al., 2010). Individuals' quality of lifes and activities in the waking hours are greatly affected by the quality of sleep (Jeong et al., 2015; Wilson et al., 2019) and reciprocally, daily stressors increase later bedtimes, poorer sleep, and more mental health difficulties in older adolescents (Alvaro et al., 2014). Since SPs increase negative health outcomes (McGlinchey & Harvey, 2015) such as depression (Hickie et al., 2013; Liu & Chung, 2015), more concentration on this scope can be fruitful in the field of health and well-being. It could be also very worthwhile in promoting the understanding of the role of sleep beliefs and how they relate to sleep disorders (Jeong et al., 2015). On this point, the accessibility of a psychometric instrument is very useful as it allows the discovery of the wrong sleep beliefs and measuring behaviors and cognitions incompatible with sleep. The researchers highlight that psychometric instruments for CT and sleep are already sufficient for a thorough analysis (Di Milia et al. 2013; Loureiro & Garcia-Marques, 2015) because people seem to have the ability to recognize and assess their own CT. Therefore, cognizance of individual distinctions in CTs can be very operational in planning training programs and preventative health-associated methods for each one (Nasiri et al., 2019).

SPs are related to a higher postponed remedy of depressive disorders (Müller et al., 2016a). The impact of depressive disorders on public health due to more disabilities, morbidities, premature mortalities (Whiteford et al., 2013; Ferrari et al., 2014), and more suicidalities (Isometsä, 2014; Schaffer et al., 2015) is clear. So, timely interferences may reduce the malicious factors that affect SPs (Robillard et al., 2014; Bartel et al., 2016). Furthermore, problems in CR may cause SUD (Conroy & Arnedt, 2014) and sleep-wake disruptions increase the risk of relapse and poorer QOL in people with severe mental disorders, especially MDD, SZ, and SUD patients (Bei et al., 2015; Robillard et al., 2015). Regular treatments for severe mental disorders like psychosis has some demerits despite some merits. These treatments lead to an insight into the disorders and subsequently the poorer QOL, depression, and suicidality (Boyer et al., 2012, Ehrminger et al., 2019). Up to 50% of SZ patients may have a history of suicide attempts (Bani-Fatemi et al., 2016). In this line of research, another recent study also showed that suicide attempts among SZ patients are high, up to 11.3% (Wang et al., 2020). Among all risk factors to suicide in SZ patients (Hor & Taylor, 2010), depression, frustration, family history (Cassidy et al., 2018), and comorbidity with SUD (Adan et al., 2017c; Østergaard et al., 2017) are the important ones. The assumption is that depression occurs after the improvement of insight in psychotics and then patients view the impact

of these disorders on their QOL, which decreases significantly leading to the occurrence of suicide attempts (Lincoln et al., 2007). In short, timely interventions are required to prevent further problems.

Deaths due to homemade substances such as alcohol poisoning are caused by a lack of monitoring and quality control and strict prohibitions of use in Iran (Samadi et al., 2017). Moreover, almost SUD patients have additional mental illness and vice versa (Szerman et al., 2013). Conventional therapies (Goldsmith & Garlapati, 2004; Jones & McCance-Katz 2019) and psychiatric drug treatments for SUD and SUD comorbid severe mental illness are not promising because of the probability to substance relapse (McLellan et al., 2005; Andersson et al., 2019) and change of body's biological clock (Allebrandt et al., 2014), respectively. Therefore, the best treatment for DD patients calls for awareness of their comorbid mental disorders and contrariwise (Bootzin & Stevens, 2005; Szerman et al., 2013).

Furthermore, having two comorbid disorders as SUD+MDD and SUD+SZ seems to be hard for asking support or attaching social communication. Therefore, the results emphasize that integrating treatment strategies especially for DDs or SUD alone are long-term goals that need to be considered (Marquez-Arrico et al., 2019b). In other words, since patients with DP display a higher psychopathological problem compared with the patients with a single disorder (Brown et al., 2011; Torrens et al., 2015; Marquez-Arrico et al., 2019b), onset and continuation of the treatment are affected by both mental disorders and SUD in these patients (Brown et al., 2011; Benaiges et al., 2012). Timely involvement in a person's illness while helping to reduce SUD has a better chance of recovery, reducing relapse rates, and improving functions (Foulds et al., 2015). Since the first systematic review evaluating interventions aiming to reduce self-harm or preventing suicide among SUD patients has found little evidence of an effective intervention or treatment (Padmanathan et al., 2020), a much more cost-effective prevention program is needed for reducing the risk of these serious problems (Ialongo et al., 2001). Maintaining good sleep hygiene, sanitation in sleep, and CR organization are good ways to support this idea to have better intellectual, emotional performance (Asarnow et al., 2014), more mental health (Owens, 2014; Zhang et al., 2018), and stronger comfort system functions (Moreno-Casbas et al., 2014). Since the type of substance use can affect the occurrence of mental disorders (Mortazavi et al., 2015), the research into SUD and DD is of great importance, there is a long way to go for their better understanding

of social and background problems. Therefore, this thesis aims to draw further attention to CR and its components, which in turn should be considered as promising and worthy guidance for further non-pharmacological innovative therapies of SUD and DDs. To the best of our knowledge, this thesis is the first study on the SUD patients with and without SZ and MDD, along with a revision of their CR, QOL, and sleep beliefs in Iran. We hope this research leads to other extensive investigation projects in the area of CRs and other disorders related to SUD.

2.2. Objectives

The main objective of this study is to explore the characteristics and differences among SUD, SUD+ SZ, and SUD+MDD in Iranian patients under treatment in their clinical state.

Our secondary objectives are:

1) Investigate the epidemiological (age, marital status, socioeconomic status, academic and employment status) and clinical characteristics (age of onset of SUD, concomitance organic pathology status, personal psychiatric history, suicide attempts, type of substance use, history of SUD in the first family, legal or labor problems status, and family problems) in SUD, SUD+SZ and SUD+MDD patients.

2) Assess the circadian functioning (CT, sleep characteristics and SJL) in SUD, SUD+SZ and SUD+MDD groups.

3) Determine the differences in circadian functioning among SUD, SUD+SZ and SUD+MDD groups to establish the possible influence of comorbidity on the results.

4) Investigate the QOL dimensions including physical health, psychological health, social relationship and environmental health in SUD, SUD+SZ and SUD+MDD patients to find the possible influence of comorbidity on the results.

5) Create the Persian version of the Sleep Beliefs Scale (SBS) and present the psychometric properties in a sample of SUD patients with and without comorbid severe mental illness.

6) Explore the relationship among clinical state, circadian functioning, QOL and sleep beliefs, in each group (SUD, SUD+SZ, and SUD+MDD) and compare them in order to find the influence of comorbidity.

2.3. Hypothesizes

1) Epidemiological data (age, marital status, socioeconomic status, academic and employment status) would be different in SUD+MDD, SUD+SZ and SUD groups.

2) Clinical data including concomitance of organic pathology, personal psychiatric history, suicide attempts, polydrug use, history of SUD in the first family, legal, labor, younger age of onset of SUD and family problems would be higher in DDs in comparison to SUDs.

3) In terms of circadian functioning, ET and SJL would be more reported in the DD patients than the SUD patients.

4) Quality of sleep and its characteristics including sleep quality, sleep latency, sleep duration, sleep disturbance, sleep efficiency, sleep medication and daytime dysfunction would be worse in DDs (SUD+MDD and SUD+SZ) groups in comparison to SUD group.

5) QOL and dimensions including physical health, psychological health, social relationship and environmental health of SUD patients would be higher in comparison with SUD comorbid MDD and SZ groups.

6) According to beliefs of sleep, the SUD patients would be reported more correct beliefs than to SUD+MDD and SUD+SZ patients.

3. METHODS

3.1. Participants

This population of the study included the outpatients referred to a psychiatric and an addiction center in Shiraz, Iran. The patients were selected from these medical centers according to their diagnoses following the DSM-5 (APA, 2013). Each diagnosis was confirmed in the first evaluation session by two trained clinical psychologists and psychiatrist affiliated to Specialist Psychiatric Center and Center of Addiction Treatment. Participants providing informed consent and meeting the following criteria were included in the study. These criteria include (1) current SUD in remission for at least one month with dependence to several drugs (alcohol is missing because, in Iran, people do not often use it for the sake of culture and illegality), (2) age between 18 and 55 years, (3) male gender, (4) lack of SUD relapses for at least a month before participation, (5) current diagnosis of psychotic disorder SZ for SUD+SZ patients, (6) current diagnosis of MDD in SUD+MDD patients, (7) being under treatment and in clinically stable psychiatric symptomatology, and (8) fluent in Persian language and native of Iran. The exclusion criteria were (1) having a current substance-induced psychiatric disorder or a psychiatric disorder due to a medical condition according to DSM-V criteria, (2) uncontrolled unstable or psychiatric symptomatology, (3) inability to complete instruments, and (4) not receiving electroconvulsive therapy within 12 months before their study participation.

The final sample consists of 238 patients, all men (38.14 ± 10.11 years) given the higher prevalence of diagnostic studies for this sex. The sample collected included 81 SUD patients, 75 SUD+ SZ patients, and 82 SUD+MDD patients. From initially derived samples (n = 255), 17 patients were discarded due to not meeting the diagnostic and clinical criteria, and none of the patients included in the study were dropped. The participants included in the study accepted to participate and fill out all the information required on the questionnaires to make us collect information on sleep, sleep beliefs, QOL and CT together, with a structured interview and clinical information. Data collection was carried out during 2017-2019. Figure 5 shows the trend of included patients in SUD, SUD+MDD, and SUD+SZ groups.

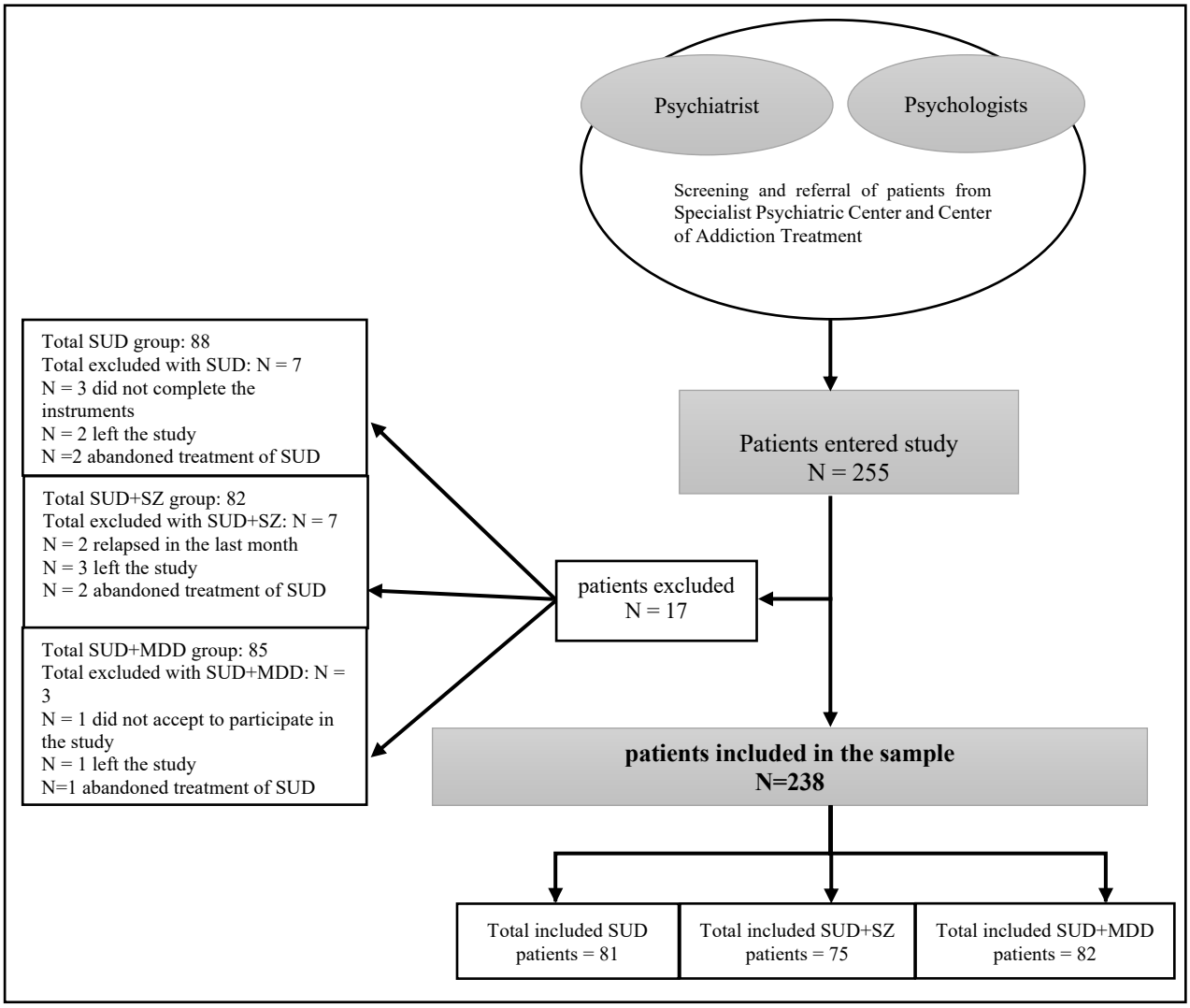


Figure 5. The patients included in the study for SUD (Substance Use Disorder), SUD+MDD (Substance Use Disorder Comorbid Major Depressive Disorder) and SUD+SZ (Substance Use Disorder Comorbid Schizophrenia) groups.

Both centers considering in this study including Specialist Psychiatric Center and Center of Addiction Treatment, are private and operating in Shiraz. The former is a specialized psychiatric center for treating the entire spectrum of psychiatric disorders and the latter is a therapeutic center for the treatment of addiction. All patients were in treatment for their clinical conditions (SUD, SUD+SZ and SUD+MDD), with an integrated intervention in which addiction and mental health treatment are offered at the same time and by the same team (De Witte et al., 2014). Integrated intervention includes a combination of motivational interviewing, contingency and case

management, cognitive behavioral therapy, social skills training and relapse prevention**.** This study was approved by the ethics committee of Shiraz University of medical sciences (SUMS) (see Annex 1) and was conducted in accordance with the ethical principles of the Helsinki Declaration (World Medical Association, 2009) and the international ethical standards of chronobiological research (Portaluppi et al., 2010). All selected participants provided written informed consent (see Annex 2) and were not compensated for their participation.

3.2. Procedure

Following the diagnosis, the research conditions were explained individually and thoroughly to each patient by the clinical psychologist, and all of them agreed on the study with satisfaction and willingness. Due to many questions in the mentioned questionnaires and the structured interview, the session for all questions took 2 days and was conducted in two 2-hour sessions for every patient and assessed individually in all cases. At first, the patients were divided into 3 groups, namely SUD, SUD+ SZ, and SUD+MDD, based on the confirmatory diagnostic interview according to DSM-5 criteria (2013). On the first day, the participants were asked about sociodemographic (e.g. age, marital status, social class, education, and economic status, and employment status) and clinical variables (e.g. diagnosis, age of onset of the SUD, type of drug use, suicide attempts, presence of organic pathology, personal psychiatric history, and legal and family problems) Clinical data were extracted and reviewed from the medical history of relevant centers and sociodemographic data were extracted from participants personally. Then, SUD+SZ patients completed the PANSS and SUD+MDD patients completed the HAMD-17 scale to determine the severity of their severe mental illness.

To save time, instead of using the Munich Chronotype Questionnaire (MCTQ), we used a short questionnaire that was prepared for SJL, was evaluated by an interview and calculated as the differences between mid-sleep on workdays (MSW) and free days (MSF) (Wittmann et al., 2006; Allebrandt et al., 2014; Sheaves et al., 2015). The time in bed was assessed by asking the following questions: What time do you usually go to bed on workdays/free days? What time do you usually wake up on workdays/free days? From these questions, the time in bed during weekdays and weekends was estimated. First, to calculate mid-sleep, the middle points of time in bed on free

days (MSF) and workdays (MSW) were calculated. Then, the middle points of between bedtime and waking time was used (Roenneberg et al., 2003).

On the second day, we assessed circadian functioning, sleep beliefs, and QOL. For this purpose, each patient filled out the rMEQ, SBS, PSQI, and WHOQOL-BREF questionnaires. The recorded results of the patients were forwarded to the psychiatrist of the center as a complement to medical history. It is of note that two clinical psychologists were assisting patients in resolving any problems concerning answering the questions (given the level of patient's literacy). Figure 6 shows the executive protocol in the SUD, SUD+MDD, and SUD+SZ groups.

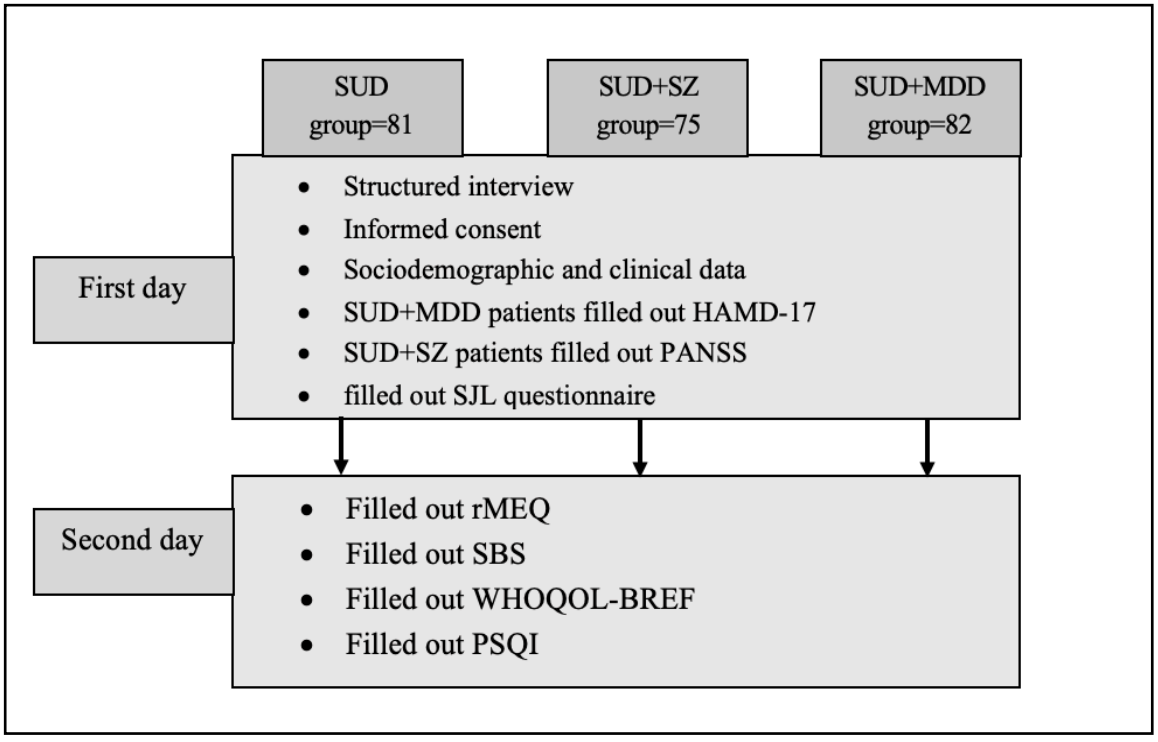


Figure 6. The executive protocol for SUD (Substance Use Disorder), SUD+MDD (Substance Use Disorder comorbid Major Depressive Disorder) and SUD+ SZ (Substance Use Disorder comorbid Schizophrenia) patients groups.

3.3. Instruments

3.3.1. Structured Interview and clinical symptomatology assessment

All selected patients were chosen by an experienced psychiatrist and two skilled clinical psychologists, separately and privately, based on the DSM-5 (APA, 2013). All patients were first visited by the psychiatrist for clinical trials and then referred to the first clinical psychologist for the second clinical interview based on DSM-5 again for further investigation. Afterward, they were referred to the last psychologist to conduct a third clinical interview for a definitive diagnosis of the disorders of SUD, SUD+SZ, and SUD+MDD (the main disorder or the cause of referral to the treatment center should be one of these three conditions).

- Hamilton Depression Rating Scale (HAMD-17)

Hamilton Rating Scale for Depression was designed to be used by healthcare professionals during a clinical interview with an already identified presence of depression symptoms. This scale is used to assess the severity of depression or as screening before diagnosis. Hamilton (1967) introduced a questionnaire with 21 items and a reviewed proposal in 1967 containing 17 items (HAMD-17). The scale is widely available with two versions of 17 or 21 questionnaires, scored between 0 and 4 points (Sharp, 2015). Hamilton in some studies reported the reliability of the HAMD-17 questionnaire through a correlation coefficient, inter-ratter reliability from 0.900 to 0.940, and validity ranging from 0.60 to 0.84 on the correlation with other instruments. Ebrahimi et al. (2013), using test-retest analysis, reported the reliability of the HAMD-17 from 0.850 and 0.891 in Iran. The HAMD-17 total score ranges from 0 to 53 and it is interpreted as follows: 0 to 7, complete recovery; 8 to 13, mild depression; 4 to 18, moderate depression; 19-22, severe depression, and >23, severe depressive symptoms. The internal reliability for the HAMD-17 in the present study was also adequate (Cronbach $\alpha = 0.793$).

- Positive and Negative Syndrome Scale (PANSS) for Schizophrenia

The PANSS Scale created by Kay et al. (1987) consists of a semi-structured 30-item interview. This scale is now one of the most broadly used questionnaires in evaluating the severity of SZ and psychotic symptomatology (Jiang et al., 2013). It consists of three subscales: The Positive syndrome (7 items), Negative syndrome (7 items), and General Psychopathology (16 items) (in the Persian version, this

subscale has been converted into the three other subscales; Disruption, Excitement and Depression-anxiety). Each of the 30 items is supplemented by a specific definition, as well as detailed anchoring points for each of the seven possible rating points. The seven rating points represent increasing levels of psychopathology (1- absent; 2- minimal; 3- mild; 4- moderate; 5- moderately severe; 6- severe; and 7- extreme) (Kay et al., 1989). This scale has been translated and used broadly in the world, both for clinical and research proposes.

In Iran, the reliability of PANSS was reported to be between 0.711 (Amini et al., 2009) and 0.802 (Abolghasemi, 2007). Furthermore, in a study by Ghamari et al. (2010) on 150 SZ spectrum disorder patients (84 with SZ and 66 with schizoaffective), it was found that 47.1% of disorders were correctly classified by the PANSS scale with the reliability of 0.770. Internal reliability for PANSS and its dimensions in our study was adequate (Positive symptoms $\alpha = 0.713$; Negative symptoms $\alpha = 0.729$; Disruption $\alpha = 0.715$; Excitement $\alpha = 0.731$; Depression-anxiety $\alpha = 0.705$; and Total PANSS $\alpha = 0.813$).

3.3.2. Circadian functioning assessments

- Social jet-Lag (SJL)

The SJL was assessed by asking four questions from the patients. In this regard, patients were asked by simple opening questions about bedtimes on free days (BTF) and bedtimes on workdays (BTW) according to their sleep-wake-cycle habits. Also, usual waketimes during the week and weekends, time to wake up during workdays (WUW), and time to wake up during the free days (WUF) were questioned. Finally, SJL was operationalized by calculating the absolute difference between mid-points of sleep on BTF /WUF and BTW/WUW (Wittmann et al., 2006).

- Reduced Morningness–Eveningness Questionnaire (rMEQ)

The CT usually is measured by the rMEQ questionnaire (Adan et al., 2012; Escribano & Díaz-Morales, 2016), a reduced instrument created from the MEQ that is composed of five items. These items deal only with morning activities and rMEQ was considered a ‘pure’ measure of morning CT (Di Milia et al., 2013). The scores range from 4 to 25 with higher scores indicating a stronger

change to MT. Adan & Almirall established the cut of the three CTs as follows: 4-11 as ET, 12-17 as IT, and 18-25 as MT. In Iran, the Persian rMEQ was developed by Rahafar et al. (2015) showing adequate reliability ($\alpha = 0.710$) and validity. The shortness and psychometric properties of rMEQ have led to its use in several countries such that it has been recently admired by several references (Di Milia et al., 2013). In the present study, the rMEQ score showed appropriate internal reliability with a Cronbach's alpha coefficient of 0.707.

- Pittsburgh Sleep Quality Index (PSQI)

PSQI is a self-report questionnaire developed by Buysse et al. (1989) that evaluates seven dimensions of sleep: subjective quality, latency, duration, usual efficiency, SPs, medication use, and daytime dysfunction. A score greater than 5 is suggestive of a sleep disorder. PSQI has internal consistency and a reliability coefficient (Cronbach's alpha) of 0.83 (Buysse et al., 1989). This scale has been translated into 56 languages and it investigates individual attitudes about sleep in the last four weeks. It has seven scores: a general description of the sleep quality, delays in falling asleep, sleep duration, sleep efficiency, sleep disorders, amount of sleep drug intake, and morning performance (Smyth, 1999; Afonso et al., 2014; Inomata et al., 2014; Zanini et al., 2015). In this sense, some of the items are open-ended responses and other questions are four-point Likert scales (Gobin et al., 2015).

Each scale of the questionnaire takes a score from zero to three. On each scale, a score of 0 indicates a normal status, of 1 a mild problem, of 2 a moderate problem, and of 3 a severe problem. All scores together range from 0 to 21. A total score of 5 or more indicates that the quality of sleep is inappropriate (Buysse et al., 1989). Internal consistency, construct validity, sensitivity and specificity of the PSQI were assessed by Moghaddam et al. (2012) in Iran, considering healthy individuals and psychiatric patients with primary insomnia, SZ, MDD, and general anxiety disorder. They accepted that the psychometric properties of the Persian version of PSQI were acceptable and reported that Cronbach's alpha coefficient for all subjects was adequate (0.701). In the present study, the Cronbach's alpha coefficient for the total PSQI score was also acceptable (0.710).

– Sleep beliefs scale (SBS)

Several studies proposed that individual beliefs can impact sleep. Therefore, SBS was created to assess one's knowledge about the effect of drug consumption (alcohol, caffeine, nicotine and sleep medication) on sleep, diurnal behaviors (physical exercise and naps), and actions and thoughts before sleep (eating, studying, relaxing, and worries). The scale, based on Sleep Hygiene Awareness by Lacks and Rotert (1986), reports the neutral, positive, or negative outcome beliefs and behavior regarding the quality and/or quantity of sleep. Adan et al. (2006) collected data from 510 undergraduate psychology students (182 men and 328 women). In this study, the questions were structured to address general beliefs and not those of an individual, to obtain the maximum number of answers possible.

SBS questionnaire contains 3 dimensions: Sleep-incompatible behaviors (eight items: 1, 2, 7, 8, 11, 17, 14 and 12), Sleep-wake-cycle behaviors (seven items: 5, 10, 16, 20, 4, 3 and 19) and Thoughts and attitudes to sleep (five items: 6, 9, 18, 13, 15). Answers from all items range from 0 to 20 and higher scores were related to better beliefs, except for items 5, 9, 15 and 19, which have a positive effect on sleep. SBS is a self-rating questionnaire and the Persian language version has not yet been created. We translated it into Spanish version of SBS (Adan et al., 2006) into Persian (see Annex 4) and then back-translated into Spanish to ensure the accuracy of the translation. Therefore, to assess the accuracy and structural validity of the questionnaire, two psychiatrists and three experimental clinical psychologists cooperated with us. The SBS showed good psychometric properties with an internal consistency for the sample studied in the present thesis of 0.725.

3.3.3. WHOQOL-BREF

Despite numerous questionnaires conducted on the QOL, yet few provide as much data as desired across different nations, languages, countries, and populations. Among these questionnaires, one which was developed by World Health Organization quality of life (1995) serves to self-appraise the QOL of healthy populations and those who are in distress due to caregiving tasks. WHOQOL-BREF was established as a brief version of the World Health Organization QOL assessment referred to as the WHOQOL-100. The instrument was developed by testing responses from over 10,000 participants and reported psychometric properties of internal consistency and proper

validity. It also consisted of a cross-cultural instrument measuring four scopes of QOL that involved physical, psychological, social, and environmental fields. The shorter version includes 26 items and encompassed four major domains of QOL: physical health, mental health, social relationships, and environment (Shawver et al., 2016).

In addition, the WHOQOL-BREF includes two items that are related to the general QOL and to the general health status of the respondent (overall QOL). Scores for each item range from 1 to 5, with higher scores indicating better QOL (Afonso et al., 2014; Shawver et al., 2016). The total scores for each field are as follows: physical health from 7 to 35, psychological health from 6 to 30, social relations from 3 to 15, and environment health from 8 to 40. This questionnaire has been translated into many languages, including Persian (Nedjat et al. 2008). The Persian version met the reliability standards in all domains (Cronbach's alpha and intra-class correlation > 0.7) and offered preliminary evidence of the test-retest reliability and validity conducted on 1167 people in Tehran. The reliability of the test-retest for the subscales was as follows: 0.770 for physical health, 0.770 for psychological health, 0.750 for social relations and 0.840 for environmental health (Nedjat et al., 2008). Reliability for 26 items of WHOQOL-BREF was also adequate in the present study (α=0.906).

3.4. Statistical analysis

Descriptive statistics (i.e., mean, standard deviation and frequencies) were calculated to describe the total sample and for each group. Group differences in demographic and clinical variables were explored with ANOVA or Kruskal-Wallis test for continuous variables and the Chi-square test for categorical variables. If the quantitative data fulfilled the necessary conditions, the ANOVA test was used; otherwise, the nonparametric Kruskal-Wallis test was used instead. Internal consistence by Cronbach's alpha coefficient was calculated for the WHOQOL-BREF, rMEQ, PSQI and SBS scales and dimensions.

Intergroup differences for the total scores of the rMEQ and PSQI scales, considering the SUD, SUD+MDD and SUD+SZ diagnoses, were examined by univariate analyses of covariance (ANCOVA). In this process, the group was considered as an independent variable and age as a covariate, since it could be a confounding factor. Also, a second ANCOVA analysis was performed

adding the age of onset of SUD as the covariate. Intergroup differences for the parameters of SJL, WHOQOL and SBS, considering the SUD, SUD+MDD and SUD+SZ groups, were examined by multivariate analyses of covariance (MANCOVA), where the group was considered an independent variable and age as a covariate. Besides, a second MANCOVA analysis was also performed adding the age of onset of SUD as covariates. To investigate differences of CTs in WHOQOL, SBS, and their dimensions, we performed MANCOVA analyses adding as factor the CT. Moreover for the total scores of PSQI, we performed ANCOVA test by considering age as covariate, and CT and the group as independent factors for both analyses. Moreover, the differences between levels of PSQI dimensions on WHOQOL-BREF dimensions were examined by MANCOVA tests, considering age as a covariate and PSQI dimensions and group as independent factors. In all cases, post-hoc analyses were Bonferroni corrected and partial Eta-square (η_p^2) was estimated to measure the effect size.

The internal reliability of the SBS was estimated by the unstandardized unit-weighted Cronbach's coefficient. An exploratory factorial analysis was performed to see common underlying factors that might be used to organize the 20 items of the SBS. This analysis displayed three independent subdimensions (Kaiser- Meyer-Olkin = 0.758). Moreover, an orthogonal varimax rotation method was carried out to simplify the interpretation. To optimum components loading, a second exploratory factorial analysis was performed after eliminating 7 items (Kaiser- Meyer-Olkin = 0.764). The analyses were carried out considering the 20 items of the original proposal and the new "reduced" SBS.

The relationships of quantitative clinical variables with rMEQ, PSQI dimensions, WHOQOL dimensions, and SBS dimensions were measured using bivariate correlation analysis. Then, only significantly related variables were entered into the subsequent multiple linear stepwise regression analysis. The relationship between the total scores of QOL and PSQI were measured by Pearson correlation. All analyses were performed using the SPSS (Statistical Package for the Social Sciences version 26.0) software. The tests were two-tailed with the type I error set at 5%.

4. RESULTS

4.1. Sociodemographic and clinical characteristics

According to Table 7, groups were not significantly different in socioeconomic and employment status. However, the ANOVA test showed a statistically significant age difference among the groups. The Post-hoc test showed that SUD+SZ patients are younger than SUD ($p<0.05$) and SUD+MDD ($p<0.05$) patients. Differences in marital status also were revealed among groups ($p<0.05$). SUD+SZ group reported a higher rate of single patients compared to SUD+MDD ($p<0.01$) and SUD groups ($p<0.05$). Considering the academic class, the chi-square test revealed a significant difference among the three groups ($p<0.01$). SUD+MDD group presented a higher rate of illiterate patients compared to both SUD ($p<0.01$) and SUD+SZ ($p<0.05$) groups. SUD+SZ group presented a higher proportion of middle school degree in comparison with SUD ($p<0.01$) and SUD+MDD ($p<0.05$) groups. In terms of college education, statistically significant differences were observed among the groups ($p<0.001$). The number of college-graduated individuals was higher in the SUD group compared with SUD+MDD ($p<0.01$) and SUD+SZ ($p<0.05$) groups.

Table 7. Sociodemographic variables for the total sample and SUD (substance use disorder), SUD+MDD (substance use disorder comorbid major depressive disorder) and SUD+SZ (substance use disorder comorbid schizophrenia) groups. Mean, standard deviation, the frequency with percentage, and statistical contrast (ANOVA or Chi-Square test).

Sociodemographic data	Total	SUD	SUD+MDD	SUD+SZ	Statistical contrast
Age	38.14 ± 10.11	39.65 ± 10.19	38.94 ± 9.54	35.63 ± 10.28	$F_{(2,422)} = 3.550$*
Marital status					$x_6^2 = 16.680$*
Single	63 (26.5%)	20 (24.7%)	12 (14.6%)	31 (41.3%)	$x_2^2 = 8.667$*
Married	150 (63%)	50 (61.7%)	62 (75.6%)	38 (50.7%)	$x_2^2 = 5.760$
Divorced	16 (6.7%)	8 (9.9%)	5 (6.1%)	3 (4%)	$x_2^2 = 2.375$
Widow/Widower	9 (3.8%)	3 (3.7%)	3 (3.7%)	3 (4%)	$x_2^2 = 0.001$
Socio economic status					$x_6^2 = 11.660$
High	40 (16.3%)	17 (21%)	10 (12.2%)	13 (17.3%)	$x_2^2 = 1.850$
Middle	99 (41.6%)	33 (40.7%)	39 (47.6%)	27 (36%)	$x_2^2 = 2.182$
Middle low	69 (29%)	16 (19.8%)	24 (29.3%)	29 (38.7%)	$x_2^2 = 3.739$
Low	30 (12%)	15 (18.5%)	9 (11%)	6 (8%)	$x_2^2 = 4.200$
Academic class					$x_8^2 = 35.770$**
Illiterate	39 (16.4%)	11 (13.6%)	22 (26.8%)	6 (8%)	$x_2^2 = 10.308$*
Primary studies	43 (18.1%)	11 (13.6%)	14 (17.1%)	18 (24%)	$x_2^2 = 1.721$

Middle school	53 (22.3%)	15 (18.5%)	9 (11%)	29 (38.7%)	x_2^2 = 11.925*
High school	70 (29.4%)	26 (32.1%)	25 (30.5%)	19 (25.3%)	x_2^2 = 1.229
University studies	33 (13.9%)	18 (22.2%)	12 (14.6%)	3 (4%)	x_2^2 = 10.364***
Employment status					x_4^2 = 5.840
Active	144 (60.5%)	49 (60.5%)	56 (68.3%)	39 (52%)	$x_2^2 = 3.042$
Inactive	76 (31.9%)	24 (29.6%)	23 (28%)	29 (38.7%)	$x_2^2 = 0.816$
Retired	18 (7.5%)	8 (9.9%)	3 (3.7%)	7 (9.3%)	$x_2^2 = 2.333$

* p<0.05; ** p<0.01; *** p<0.001

Concerning the studied clinical variables (see Table 8), the ANOVA test showed a significant age of onset of SUD difference among the groups. The Post-hoc test showed statistically significant differences among SUD+SZ and both SUD+MDD (p<0.001) and SUD (p<0.05) groups, the age of onset of SUD in SUD+ SZ patients group was earlier. In the concomitance of organic pathology, these three groups showed significant differences. SUD+MDD group showed more hypothyroidism compared with SUD+SZ and SUD groups (p<0.05, in both cases). SUD+SZs showed more seizure problems than to both SUD (p<0.01) and SUD+MDD groups (p<0.05). Moreover, in other medical disorders (hepatitis B/C, obesity, HIV, spinal problems, and diabetes) there were significant differences among groups with more presence in SUD+MDD group than the SUD+SZ and SUD groups (p<0.05, in both cases). Regarding the total medical disorders, the SUD+MDD group indicated more organic pathologies followed by SUD+SZ (p<0.05) and SUD (p<0.01) groups.

Considering the personal psychiatric history, a significant difference was observed among the groups in General Anxiety and Adjustment Disorders. SUD+ MDD patients showed more General Anxiety Disorder compared to SUD (p<0.05) but no difference with SUD+SZ group. Also, the SUD+MDD group significantly revealed a higher rate of the Adjustment disorder than to both SUD and SUD+SZ groups (p<0.001, in both cases). In other psychiatric history disorders (eating disorders, PTSD, and personality disorders), the SUD+SZ group reported more presence than the SUD+MDD and SUD groups (p<0.05, in both cases). Regarding total psychiatric personal history, the SUD+MDD group showed a higher rate of mental disorders compared with SUD+SZ (p<0.01) and SUD (p<0.001) groups. The groups also showed a significant difference in suicide attempts. SUD+MDD group had more suicide attempts in comparison with SUD (p<0.01) and SUD+SZ groups (p<0.001). In the field of law or legal problems, SUDs reported more conflicts compared to SUD+MDD (p<0.001) and SUD+SZ groups (p<0.05).

According to the type of substance use, there were differences among groups in the types of substance use. In this respect, the SUD group reported the highest rate of opium users compared to both SUD+MDD and SUD+SZ ($p<0.05$, in both cases) groups. Moreover, SUD patients reported a higher amount of crystal users compared to the SUD+MDD ($p<0.01$) and SUD+SZ groups ($p<0.05$). In return, the SUD+SZ group reported the highest proportion of heroin users in comparison to SUD+MDDs ($p<0.05$), although with no difference with the SUD group. Moreover, ANOVA analysis also revealed significant mean differences in the number of substance use among groups ($p<0.001$). The SUD+SZ group had higher numbers of substance use, followed by SUD+MDD ($p<0.01$) and SUD ($p<0.05$) groups, in order of their appearance. Also, groups were different in polydrug consumption. More rate of polydrug use was observed in the SUD+SZ patients in comparison with SUD+MDD ($p<0.01$) group but no significant difference with the SUD group. Clinical data in relation to substance use consumption including the age of onset of SUD, medical and other psychiatric histories, presence of SUD in the first-degree relative, family and legal problems and the type of substance use in the SUD, SUD+SZ and SUD+MDD patients are shown in Table 8.

Table 8. Clinical characteristics for total sample and SUD (substance use disorder), SUD+MDD (substance use disorder comorbid major depressive disorder) and SUD+SZ (substance use disorder comorbid schizophrenia) groups. Mean, standard deviation, the frequency with percentage and statistical contrast (ANOVA or Chi-Square tests).

Clinical data	Total	SUD	SUD+MDD	SUD+SZ	Statistical contrast
Age of onset of SUD	34.40 ± 8.23	35.04 ± 9.22	36.37 ±10.29	30.81 ± 8.40	$F_{(10,152)} = 11.402$**
Concomitance of organi pathology status					$\chi^2_{12} = 25.630$ *
Total organic pathology comorbidity	114 (100%)	27 (23%)	49 (42%)	38 (33%)	$x^2_2 = 6.368$ *
Hypertension	9 (3.8%)	3 (3.7%)	1 (1.2%)	5 (6.7%)	$x^2_2 = 2.667$
Hypothyroidism	10 (4.2%)	2 (2.5%)	7 (8.6%)	1 (1.3%)	$x^2_2 = 6.200$*
Hyperthyroidism	10 (4.2%)	3 (3.7%)	2 (2.5%)	5 (6.7%)	$x^2_2 = 1.400$
Seizure	19 (8%)	1 (1.2%)	7 (8.6%)	11 (14.7%)	$x^2_2 = 8.000$*
Irritable bowel syndrome	8 (3.4%)	1 (1.2%)	4 (4.9%)	3 (4%)	$x^2_2 = 1.750$
Migraine	9 (3.8%)	2 (2.5%)	5 (6.2%)	2 (2.7%)	$x^2_2 = 2.000$
Other disorders (Hepatitis B/C, Obesity, HIV, Spinal problems, diabetes)	49 (20%)	15 (18%)	23 (28%)	11 (15%)	$x^2_2 = 3.896$**

Personal psychiatric history					$x_{12}^2 = 13.671^{**}$
Total personal psychiatric history	179 (100%)	35 (19.5%)	88 (49%)	56 (31%)	$x_2^2 = 23.877^{***}$
Relational Problems	23 (9.6%)	5 (6.2%)	5 (6.1%)	13 (17.3%)	$x_2^2 = 5.565$
General Anxiety Disorder	27 (11.3%)	3 (3.7%)	13 (15.8)	11 (14.6%)	$x_2^2 = 6.222^{*}$
Panic disorder	17 (7.1%)	5 (6.2%)	6 (7.3%)	6 (8%)	$x_2^2 = 0.118$
OCD	19 (7.9%)	4 (4.9%)	9 (10.9%)	6 (8%)	$x_2^2 = 2.000$
Adjustment disorder	39 (16.3%)	3 (3.7%)	36 (43.9%)	0	$x_2^2 = 27.923^{***}$
Somatic disorders	20 (8.4%)	4 (4.9%)	9 (10.9%)	7 (9.3%)	$x_2^2 = 1.900$
Other disorders (Eating disorders, PTSD, personality disorders)	34 (14%)	11 (13%)	10 (12%)	13 (17%)	$x_2^2 = 45.355^{*}$
Suicide attempts	0.34 ± 0.74	0.26 ± 0.66	0.61 ± 0.95	0.15 ± 0.39	$F_{(2,235)} = 9.066^{***}$
Presence of SUD in the first-degree relative					$\chi_{12}^2 = 1.192$
Father	30 (12.6%)	17 (21%)	6 (7.3%)	7 (9.3%)	$x_2^2 = 7.400$
Mother	12 (5%)	2 (2.5%)	8 (9.8%)	2 (2.7%)	$x_2^2 = 6.000$
Sister	5 (2.1%)	2 (2.5%)	2 (2.4%)	1 (1.3%)	$x_2^2 = 0.400$
Brother	29 (12.2%)	7 (8.6%)	16 (19.5%)	6 (8%)	$x_2^2 = 6.276$
Not considered	156 (65.5%)	53 (65.4%)	46 (56.1%)	57 (76%)	$x_1^2 = 0.200$
Presence of problems					
Legal problems status					$x_1^2 = 13.504^{**}$
Yes	22 (9.2%)	13 (16%)	0	9 (12%)	$x_1^2 = 6.077^{*}$
Labor problem status					$x_2^2 = 5.733$
Yes	45 (18.9%)	16 (19.8%)	8 (9.8%)	21 (28%)	$x_2^2 = 5.733$
Family problems					$x_1^2 = 34.034$
Yes	74 (31.1%)	23 (28.4%)	30 (36.6%)	21 (28%)	$x_2^2 = 1.192$
Type of Substance [a]					
Nicotine	162 (68.1%)	58(70.7%)	46 (61.3%)	58 (71.6%)	$\chi_2^2 = 1{,}777$
Opium	107 (45%)	45 (55.6%)	32 (39%)	30 (40%)	$\chi_2^2 = 3.719^{*}$
Cristal	68 (28.6%)	30 (37%)	14 (17.1%)	24 (32%)	$\chi_2^2 = 8.591^{*}$
Heroin	62 (26.1%)	25 (30.9%)	11 (13.4%)	26 (34.7%)	$\chi_2^2 = 6.806^{*}$
Other	67 (28.2%)	17 (21%)	27 (32.9%)	23 (30.7%)	$\chi_2^2 = 2.268$
Number of substance use	1.94 ± 0.84	2.04 ± 0.84	1.71 ± 0.75	2.08 ± 0.88	$F_{(2,235)} = 4.917^{***}$
Polydrug use	76 (32.3%)	30 (37%)	14 (17.2%)	32 (42.6%)	$\chi_4^2 = 7.684^{*}$

* p<0.05; ** p<0.01; *** p<0.001

[a] Percentages will not equal 100 as each participant may be in more than one category at the same time

HAMD-17: Hamilton depression rating scale; OCD: Obsessive compulsive disorder; PANSS: Positive and negative syndrome scale; PTSD: Post-traumatic stress disorder

The following clinical data, the characteristics of SUD+SZ and SUD+MDD patients are shown in Table 9. Evaluated SZ dimensions by PANSS indicated more negative symptoms followed by positive symptoms, disruption, depression-anxiety and excitement in this group of patients respectively. Also, this scale showed that more frequency of patients are categorized in mild SZ. According to the HAMD-17 scale, depending on the severity of the disorder, most of the patients reported moderate depression followed by severe, very severe, mild levels.

Table 9. Clinical characteristics of SUD+SZ (substance use disorder comorbid schizophrenia) and SUD+MDD (substance use disorder comorbid major depressive disorder) patients. Mean, standard deviation, the frequency with percentage.

Clinical data	SUD+SZ	SUD+MDD
PANSS	76.36 ± 27.94	
Positive symptoms	17.64 ± 9.12	
Negative symptoms	19.88 ± 9.15	
Disruption	17.01 ± 9.88	
Excitement	9.92 ± 4.74	
Depression-anxiety	11.91 ± 6.55	
PANSS category		
Mild SZ	27 (36%)	
Moderate SZ	25 (33.3%)	
Severe SZ	23 (30.7%)	
HAMD-17		18.26 ± 5.36
Normal		2 (2.4%)
Mild depression		10 (12.2%)
Moderate depression		32 (39%)
Severe depression		24 (29.3%)
Very severe depression		14 (17.1%)

4.2. Circadian functioning: Social jet-lag, circadian typology, quality and components of sleep, and sleep beliefs

4.2.1. Social Jet-Lag (SJL)

The MANOVA analysis, using age as covariate, performed to determine if there are differences among groups in terms of the SJL variables (see Table 10) showed no significant difference among SUD+MDD, SUD+SZ and SUD patients in SJL, WUW and WUF. However, the differences among groups in BTW and BTF were significant; SUD group showed a delay of BTW and BTF compared with both SUD+MDD and SUD+SZ groups ($p<0.01$, in both cases). That is to say, SUDs went to bed later than SUD+MDDs and SUD+SZs both during the workdays and the free days (weekend). In this regard, the second MANCOVA analysis, considering age and age of onset of SUD as covariates, confirmed the same result as the first analyses.

Table 10. SJL (social jet-lag) and related parameters for the total sample and SUD (substance use disorder), SUD+MDD (substance use disorder comorbid major depressive disorder) and SUD+SZ (substance use disorder comorbid schizophrenia) groups. Mean scores, stand deviation with F and partial eta square (η_p^2) (MANCOVA results).

						Age as covariate	Age and age of onset of SUD as covariates
	SUD	SUD+MDD	SUD+SZ	$F_{(2,234)}$	η_p^2	$F_{(2,233)}$	η_p^2
BTW	00.22 ± 2.10	23.50 ± 1.83	23.42 ± 1.57	6.254**	0.051	6.146**	0.050
WUW	7.73 ± 1.83	7.83 ± 1.92	7.67 ± 1.71	0.266	0.002	0.446	0.004
BTF	00.45 ± 2.34	23.50 ± 1.98	00.19 ± 1.77	4.314*	0.036	4.485*	0.037
WUF	8.82 ± 2.06	9.26 ± 1.96	9.61 ± 2.03	2.915	0.024	2.536	0.021
SJL	1.35 ± 3.40	0.39 ± 0.75	0.46 ± 0.99	2.535	0.021	2.538	0.021

* p<0.05; ** p<0.01
BTF: Bed time during the free days; BTW: Bed time during the weekdays;
WUF: Wake up during the free days; WUW: Wake up during the workdays

4.2.2. Circadian typology (CT)

According to CT, the chi-square test showed that there is a significant difference among the three groups of patients. In the distribution of the three chronotypes SUD patients were more likely to be IT in comparison with SUD+MDD and SUD+SZ groups (p<0.01, in both cases) while SUD+MDD patients were more prone to be MT compared with SUD and SUD+SZ groups (p<0.01, in both cases). Furthermore, as shown in Table 11, SUD+SZ patients were more likely to be ET compared with SUD and SUD+MDD groups (p<0 .01, in both cases). Figure 7 illustrates the percentages of chronotypes in SUD, SUD+MDD and SUD+SZ groups. There was no bivariate correlation among rMEQ and the clinical variables considered.

Table 11. Results of the CT (chronotype) for the total sample and the three groups of SUD (substance use disorder), SUD+MDD (substance use disorder comorbid major depressive disorder) and SUD+SZ (substance use disorder comorbid schizophrenia) patients. Frequencies and percentages (Chi-Square test).

Chronotype	Total	SUD	SUD+MDD	SUD+SZ	Statistical contrast $x_4^2 = 28.502^{**}$
ET	92 (39%)	22 (27%)	26 (31%)	44 (59%)	$x_2^2 = 8.950\ **$
IT	88 (37%)	43 (53%)	26 (31%)	19 (25%)	$x_2^2 = 10.381\ *$
MT	58 (25%)	16 (20%)	30 (36%)	12 (16%)	$x_2^2 = 9.241\ **$

* p<0.05; ** p<0.01

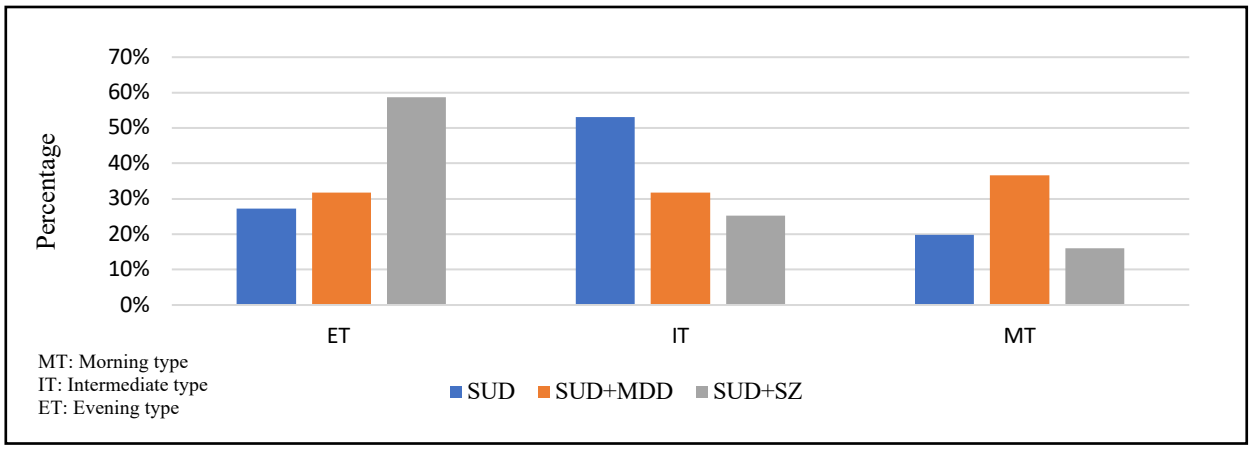


Figure 7. Chronotype percentages evaluated with rMEQ (reduced Morningness-Eveningness Questionnaire) in three groups of SUD (substance use disorder), SUD+MDD (substance use disorder comorbid major depressive disorder) and SUD+SZ (substance use disorder comorbid schizophrenia) patients.

The total score of rMEQ also showed differences among the groups in the ANCOVA analysis, using age as a covariate. According to the obtained results, SUD+SZ patients presented the lowest scores compared with both SUD (p<0.05) and SUD+MDD patients (p<0.001). The second ANCOVA analysis considering age and age of onset of SUD as covariates again revealed the same results but with lower statistical effect size among groups (see Table12). In this sense, SUD+SZ patients presented the lower scores of rMEQ compared with SUD+MDD (p<0.01) and SUD ones (p<0.05). Figure 8 presents the results of the mean scores in SUD, SUD+MDD and SUD+SZ groups along with the mean of Iranian normal population, comparing the group means with the Iranian normative data (15.05 ± 3.71) (Rahafar et al., 2015). Although SUD and SUD+SZ

groups presented lower scores, this was more evident in the SUD+SZ group (t_{147}= -4.461, p<0.001) then followed by SUD group (t_{165}= -1.840, p<0.05) while SUD+MDD group presented scores similar to norm.

Table 12. rMEQ (reduced Morningness-Eveningness Questionnaire) scores for the three groups of SUD (substance use disorder), SUD+MDD (substance use disorder comorbid major depressive disorder) and SUD+SZ (substance use disorder comorbid schizophrenia) patients. Mean scores, standard deviation with F and partial eta square (η_p^2) (ANOVA results).

				Age as covariate		Age and age of onset of SUD as covariates	
	SUD	SUD+MDD	SUD+SZ	$F_{(2,234)}$	η_p^2	$F_{(2,233)}$	η_p^2
rMEQ score	13.99 ± 3.98	14.82 ± 4.51	12.32 ± 4.23	6.789**	0.055	6.211**	0.051

** p<0.01

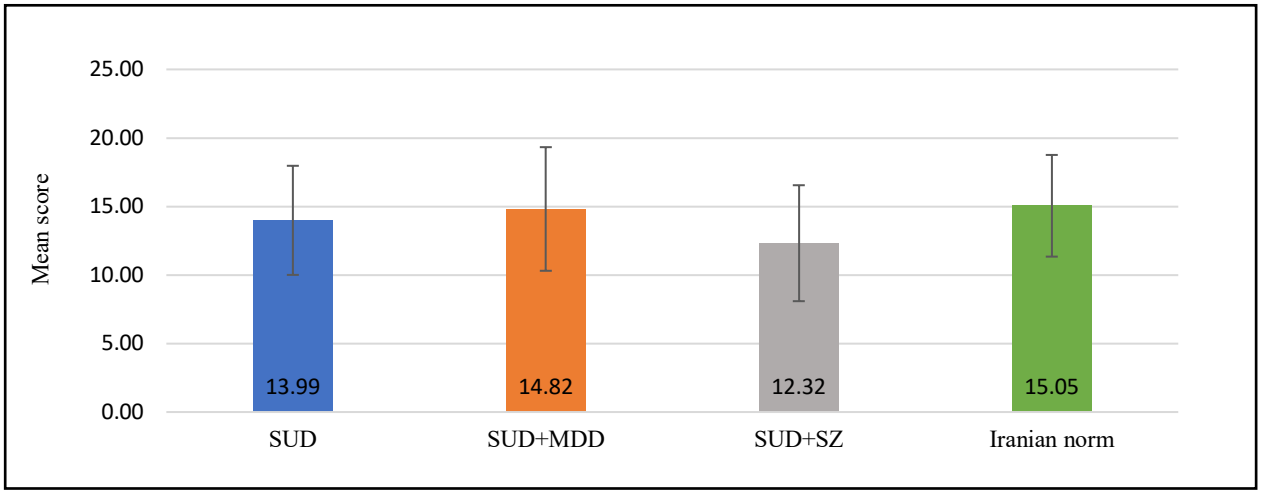


Figure 8. Mean differences of rMEQ (reduced Morningness-Eveningness Questionnaire) scores in three groups of SUD (substance use disorder), SUD+MDD (substance use disorder comorbid major depressive disorder) and SUD+SZ (substance use disorder comorbid schizophrenia) patients and the Iranian population norms.

The analysis of the relationships with the clinical variables provided that there was a significant difference of CT in polydrug consumers in the total sample and in the SUD and SUD+SZ groups (see Table 13). In SUD polydrug users, IT was more observable compared with MT and ET (p<0.05, in both cases). Also, in the SUD+SZ group, the patients with polydrug use reported more

presence of ET than of IT and MT (p<0.001, in both cases). Finally, in the total sample, also the presence of ET of the patients with polydrug use was greater than of MT (p<0.01) and IT ones (p<0.05).

Table 13. Polydrug users according to CT (chronotype) for the total sample and the three groups of SUD (substance use disorder), SUD+MDD (substance use disorder comorbid major depressive disorder) and SUD+SZ (substance use disorder comorbid schizophrenia) patients. Frequencies, percentages and Chi-Square test.

Polydrug use	Group	CT Evening type (ET)	Intermediate (IT)	Morning type (MT)	Statistical contrast
	SUD	8 (36.4%)	17 (39.5%)	5 (31.3%)	$\chi_2^2 = 7.802$*
	SUD+MDD	5 (19.2%)	2 (7.7%)	7 (23.3%)	$\chi_2^2 = 2.711$
	SUD+SZ	22 (50%)	7 (36.8%)	3 (25%)	$\chi_2^2 = 18.810$***
	Total sample	35 (38%)	26 (29.5%)	15 (25.9%)	$\chi_2^2 = 7.920$*

* p<0.05; ***p<0.001

4.2.3. Quality and components of sleep (PSQI)

In order to quality of sleep, the dimension of PSQI, the SUD+MDD group reported more fairly bad sleep quality in comparison to SUD and SUD+SZ patients (p<0.05, in both cases). Considering the sleep latency, SUDs reported the minimum time compared to SUD+MDDs (p<0.001) and SUD+SZs (p<0.05). Also, according to the efficiency of sleep levels, 65 to74% of effective sleep only was reported in SUD patients compared with two other groups (p<0.05, in both cases). In contrast, the groups did not differ in the total duration of sleep, the three contributed a majority of patients in the 5-6 hour (SUD and SUD+MDD) and in the 6-7 hour (SUD+SZ) categories.

The SUD+SZ group indicated the most disturbances in sleep in once or twice a week status in comparison with SUD and SUD+MDD groups (p<0.05, in both cases). Using medication to sleep was different among the three groups (p< 0.01). SUD group reported the lowest consumption of sleep medication during the last month compared to SUD+MDD and SUD+SZ groups (p<0.05, in both cases). In turn, sleep medication in the SUD+MDD group was more frequent than in the other two (p<0.001, in both cases). In other words, SUD+MDDs used more psychiatric drugs to fall asleep while the SUD group reported the lowest sleep medication among the three groups during

the last month (see Table 14). The percentage of dimensions and mean scores of total PSQI scores in SUD, SUD+MDD and SUD+SZ groups are shown in Figures 9 and 10 respectively.

Table 14. Quality and dimensions of sleep for the total sample and three groups of SUD (substance use disorder), SUD+MDD (substance use disorder comorbid major depressive disorder) and SUD+SZ (substance use disorder comorbid schizophrenia) patients. Frequency with percentage and statistical contrast (Chi-Square test).

PSQI	Total	SUD	SUD+MDD	SUD+SZ	Statistical contrast
Sleep quality					$x_6^2 = 14.780$*
Very good	30 (12.6%)	14 (17.2%)	4 (4.8%)	12 (16%)	$x_2^2 = 5.600$
Fairly good	116 (48.7%)	43 (53%)	39 (47.5%)	34 (45.3%)	$x_2^2 = 1.052$
Fairly bad	62 (26%)	14 (17.2%)	31 (37.8%)	17 (22.6%)	$x_2^2 = 07.968$ *
Very bad	30 (12.6%)	10 (12.3%)	8 (9.7%)	12 (16%)	$x_2^2 = 0.800$
Sleep latency					$x_6^2 = 20.900$**
Lower than 15 minutes	97 (40.8%)	46 (56.8%)	19 (23.2%)	32 (42.7%)	$x_2^2 = 11.270$ **
16-30 minutes	76 (31.9%)	18 (22.2%)	34 (41.5%)	24 (32%)	$x_2^2 = 1.064$
31-60 minutes	47 (19.7%)	14 (17.3%)	19 (23.2%)	14 (18.7%)	$x_2^2 = 0.587$
More than 60 minutes	18 (7.6%)	3 (3.7%)	10 (12.2%)	5 (6.7%)	$x_2^2 = 4.330$
Sleep duration					$x_6^2 = 11.790$
More than 7 hours	25 (10.5%)	8 (9.9%)	12 (14.6%)	5 (6.7%)	$x_2^2 = 0.228$
6-7 hours	85 (35.7%)	28 (34.6%)	20 (24.4%)	37 (49.3%)	$x_2^2 = 0.078$
5-6 hours	104 (43.7%)	36 (44.4%)	40 (48.8%)	28 (37.3%)	$x_2^2 = 0.341$
Less than 5 hours	24 (10.1%)	10 (12.2%)	9 (11.1%)	5 (6.7%)	$x_2^2 = 0.417$
Sleep efficiency					$x_6^2 = 13.731$*
More than 85%	43 (18.1%)	17 (21%)	8 (9.8%)	18 (24%)	$x_2^2 = 4.233$
75%-84%	14 (5.9%)	4 (4.9%)	8 (9.8%)	2 (2.7%)	$x_2^2 = 4.000$
65%-74%	70 (29.4%)	28 (31.4%)	22 (27%)	20 (30%)	$x_2^2 = 1.486$*
Lower than 65%	111 (46.6%)	40 (49.4%)	44 (53.7%)	27 (36%)	$x_2^2 = 4.270$
Sleep disturbance					$x_6^2 = 15.681$*
Not during past month	9 (3.8%)	5 (6.1%)	0	4 (5.3%)	$x_2^2 = 0.739$
Less than once a week	164 (68.9%)	60 (74.1%)	63 (76.8%)	41 (54.7%)	$x_2^2 = 0.074$
Once or twice a week	61 (25.6%)	17 (21%)	18 (22%)	26 (34.7%)	$x_2^2 = 0.302$*
Three or more times a week	4 (1.7%)	0	1 (1.2%)	3 (4%)	$x_2^2 = 0.317$
Sleep medication					$x_6^2 = 52.152$**
Not during past month	71 (29.8%)	35 (43.2%)	17 (20.7%)	19 (25.3%)	$x_2^2 = 8.222$ **
Less than once a week	46 (19.3%)	15 (18.5%)	3 (3. 7%)	28 (37.3%)	$x_2^2 = 20.390$ ***

Once or twice a week	19 (8%)	8 (9.9%)	5 (6.1%)	6 (8%)	$x_2^2 = 0.737$
Three or more times a week	102 (42.9%)	23 (28.4%)	57 (69.5%)	22 (29.3%)	$x_2^2 = 23.350$ ***
Daytime dysfunction					$x_6^2 = 11.441$
No problem at all	53 (22.3%)	26 (32.1%)	11 (13.4%)	16 (21.3%)	$x_2^2 = 6.604$
Only a very slight problem	83 (34.9%)	21 (25.9%)	32 (39%)	30 (40%)	$x_2^2 = 2.482$
Somewhat of a problem	80 (33.6%)	26 (32.1%)	29 (35.4%)	25 (33.3%)	$x_2^2 = 0.325$
A very big problem	22 (9.2%)	8 (9.9%)	10 (12.2%)	4 (5.3%)	$x_2^2 = 2{,}545$

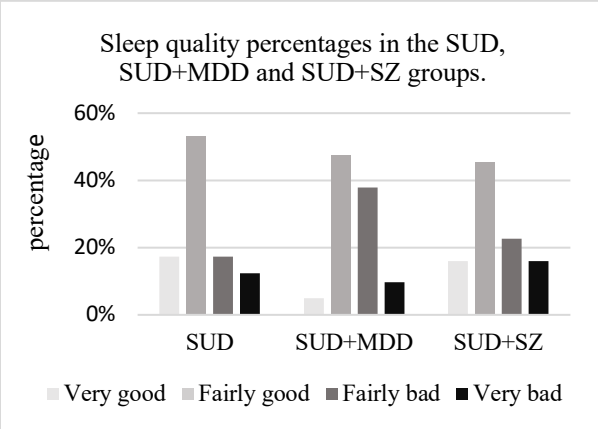
* p<0.05; ** p<0.01; *** p<0.001
PSQI: Pittsburgh sleep quality index

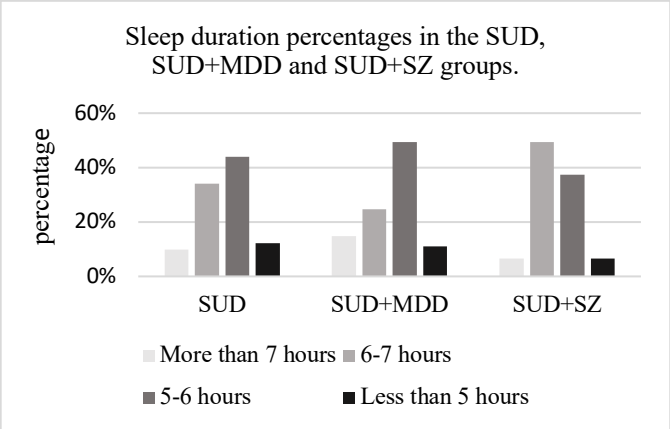
ANCOVA analyses, using age as a covariate, showed differences among groups in the total score of PSQI (see Table 15). According to the obtained results, SUD+MDD patients reached the highest scores compared with both SUD (p<0.001) and SUD+SZ patients (p<0.001). In other words, SUD+MDD group reported the worst scores in PSQI scale. In this regard, the second ANCOVA analysis considering age and age of onset of SUD as covariates confirmed the same result as the first analyses.

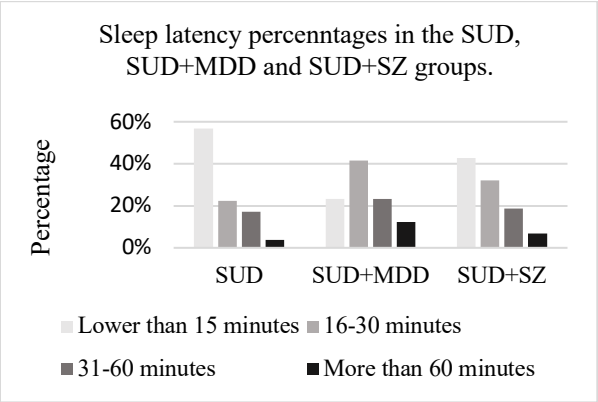
Table 15. Total PSQI (Pittsburgh Sleep Quality Index) scores for the three groups of SUD (substance use disorder), SUD+MDD (substance use disorder comorbid major depressive disorder) and SUD+SZ (substance use disorder comorbid schizophrenia) patients. Mean scores, standard deviation with F and partial eta square (η_p^2) (ANCOVA results).

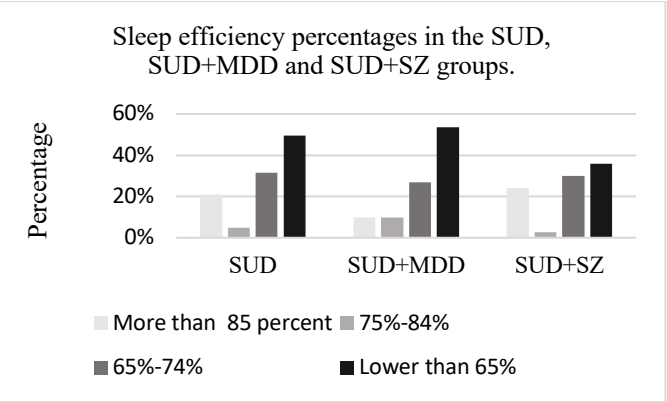
				Age as covariate		Age and age of onset of SUD as covariates	
	SUD	SUD+MDD	SUD+SZ	F	η_p^2	F	η_p^2
PSQI score	9.12 ± 2.96	11.56 ± 3.13	9.57 ± 2.42	16.453***	0.123	15.112***	0.115

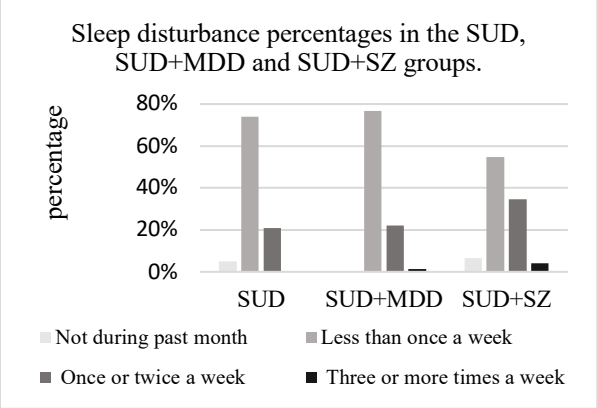
*** p<0.001

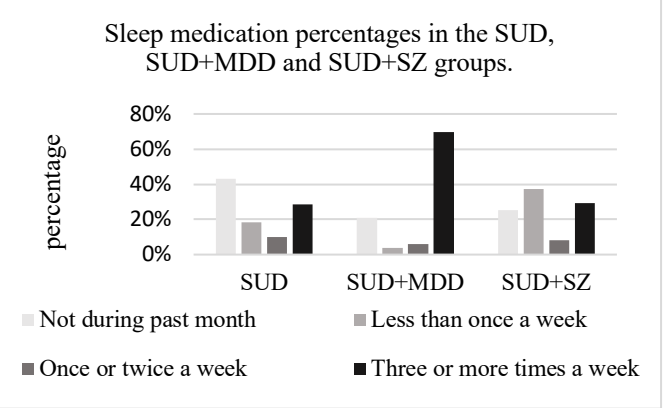

Sleep quality percentages in the SUD, SUD+MDD and SUD+SZ groups.
percentage
60%
40%
20%
0%
SUD
SUD+MDD
SUD+SZ
Very good
Fairly good
Fairly bad
Very bad


Sleep duration percentages in the SUD, SUD+MDD and SUD+SZ groups.
percentage
60%
40%
20%
0%
SUD
SUD+MDD
SUD+SZ
More than 7 hours
6-7 hours
5-6 hours
Less than 5 hours


Sleep latency percenntages in the SUD, SUD+MDD and SUD+SZ groups.
Percentage
60%
40%
20%
0%
SUD
SUD+MDD
SUD+SZ
Lower than 15 minutes
16-30 minutes
31-60 minutes
More than 60 minutes


Sleep efficiency percentages in the SUD, SUD+MDD and SUD+SZ groups.
Percentage
60%
40%
20%
0%
SUD
SUD+MDD
SUD+SZ
More than 85 percent
75%-84%
65%-74%
Lower than 65%


Sleep disturbance percentages in the SUD, SUD+MDD and SUD+SZ groups.
percentage
80%
60%
40%
20%
0%
SUD
SUD+MDD
SUD+SZ
Not during past month
Less than once a week
Once or twice a week
Three or more times a week


Sleep medication percentages in the SUD, SUD+MDD and SUD+SZ groups.
percentage
80%
60%
40%
20%
0%
SUD
SUD+MDD
SUD+SZ
Not during past month
Less than once a week
Once or twice a week
Three or more times a week

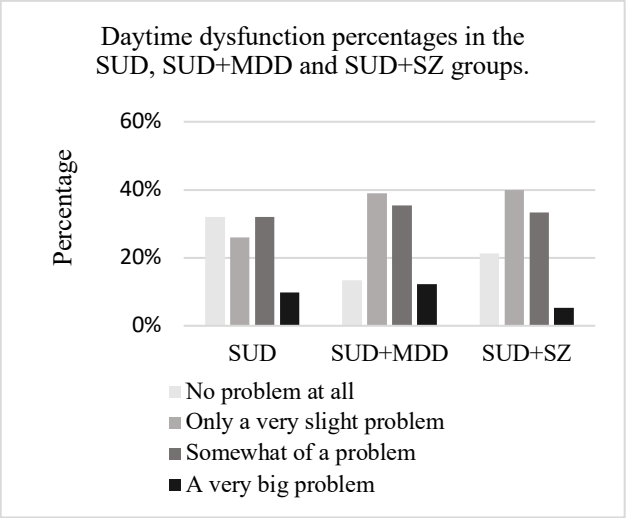


Figure 9. The percentages of PSQI (Pittsburgh Sleep Quality Index) dimensions in the groups of SUD (substance use disorder), SUD+MDD (substance use disorder comorbid major depressive disorder) and SUD+SZ (substance use disorder comorbid schizophrenia) patients.

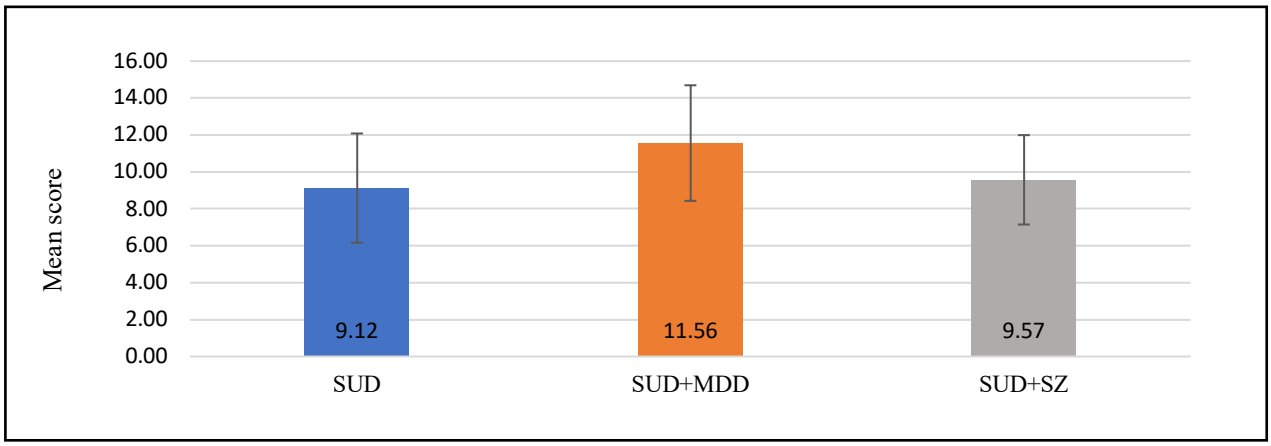


Figure 10. Mean differences of the total PSQI (Pittsburgh Sleep Quality Index) scores in the three groups of SUD (substance use disorder), SUD+MDD (substance use disorder comorbid major depressive disorder) and SUD+SZ (substance use disorder comorbid schizophrenia) patients.

Regarding the clinical variables associated with the total PSQI score, only the variables of the age of onset of SUD and HAMD-17 score were related SUD-MDD group (see Table 16). Regression analyses indicated that both the age of onset of SUD negatively, and scoring of HAMD-17 positively were related to total score of PSQI in the SUD+MDD group, explaining 5.5% of its

variance ($F_{(2,79)}$ = 5.980; p<0.05). No variables were associated with total PSQI in the SUD+SZ and SUD groups and the total sample.

Table 16. Significant linear regressions for total score of PSQI (Pittsburgh Sleep Quality Index) in SUD+MDD (substance use disorder comorbid major depressive disorder) group.

PSQI	Group	Adjusted R^2	IV	ß standardized	p value	Tolerance	VIF	Durbin Watson
Total PSQI	SUD+MDD	0.055	Age of onset of SUD	-0.265	0.017	0.985	1.020	1.995
			HAMD-17	0.259	0.019	0.985	1.020	

MANCOVA analyses indicated no interaction between CT and group in total PSQI (see Table 17). Therefore, the main effect of CT showed a significant difference in the PSQI score. ETs reported worse PSQI scores (10.60 ± 3.18) compared to ITs (9.34 ± 2.77) (p<0.01) but no difference with MTs (10.48 ± 3.07).

Table 17. Statistical value (F and η_p^2) for chronotype, group and their interaction on quality of sleep (MANCOVA results).

	Factor	F	η_p^2
Total PSQI	Chronotype	$F_{(2,228)} = 4.750$*	0.040
	Group	$F_{(2,228)} = 15.852$***	0.122
	Chronotype x Group	$F_{(4,228)} = 1.171$	0.020

*p<0.05; ***p<0.001
PSQI: Pittsburgh sleep quality index

4.2.4. Beliefs of sleep (SBS)

The mean score for the SBS was 15.65 ± 3.29; (range 1-20) in the total sample, suggesting a biased distribution to higher scores (correct beliefs) (Z = 0.177; p<0.001). The mean score of the SUD group was 15.52 ± 3.93 showing a biased distribution to higher scores (Z = 0.263; p<0.001). For the SUD+MDD group, the score was 16.46 ± 1.97 and for the SUD + SZ the score was 14.90 ± 3.52, also in both cases (SUD + MDD: Z = 0.197; p<0.001 and SUD+SZ: Z = 0.177; p<0.001) indicating a biased distribution to higher scores.

Except for the internal reliability of the total sample of SBS in our study (α = 0.725), this reliability for the three SBS dimensions as proposed in the original scale (Adan et al., 2006) was low and below the acceptable value of 0.700 in all cases of our sample: Sleep-wake-cycle behaviors (α = 0.671), Sleep-incompatible behaviors (α = 0.537) and Thoughts and attitudes to sleep (α = 0.345). The screen plot of the exploratory factor analysis of the SBS using the extraction method of principal components indicated that three dimensions with an eigenvalue >1.3 should be retained, accounting for 31.1% of the total sample variance (F1 = 13.8%, F2 = 10.2%, F3 = 7.1%). The orthogonal Varimax rotation final solution is presented in Table 5, where all the items are grouped in the three factors. The first factor, "Sleep-wake-cycle behaviors", was composed by eleven items (item 2, item 3, item 4, item 5, item 6, item 7, item 13, item 15, item 17, item 18 and item 19); the second factor, "Sleep-incompatible behavior ", included six items (item 8, item 10, item 11, item 12, item 14 and item 16) and the third factor, "Thoughts and attitudes to sleep", was composed by three items (item 1, item 9 and item 20) (Table 18). All three dimensions (Sleep-wake-cycle behaviors (ρ = 0.749, p<0.01), Sleep-incompatible behaviors (ρ = 0.655, p<0.01) and Thoughts and attitudes to sleep (ρ = 0.392, p<0.01) correlate significantly with the total score of the SBS. Moreover, in the total sample, the mean score for the Sleep-incompatible behaviors was 4.74 ± 0.09; (range 0-6), for Sleep-wake-cycle behaviors was 8.64 ± 0.14; (range 1-11), and for Thoughts and attitudes to sleep was 2.26 ± 0.05; (range 0-3), suggesting a biased distribution to higher scores (correct beliefs) in all three cases: Sleep-incompatible behaviors (Z = 0.231; p<0.001), Sleep-wake-cycle behaviors (Z = 0.213; p<0.001) and Thoughts and attitudes to sleep (Z = 0.270; p<0.001).

Table 18. Internal reliability (Cronbach's α) for all 20 items of the scale (if one item is deleted) and principal component analysis: Varimax rotated final solution where loadings in bold identify the factor to which the item was assigned. Mean scores and standard deviation in the total sample and the three groups of SUD (substance use disorder), SUD+MDD (substance use disorder comorbid major depressive disorder) and SUD+SZ (substance use disorder comorbid schizophrenia) patients.

Item	α	F1	F2	F3
1. Drinking alcohol in the evening	0.742	0.074	-0.069	-0.355
2. Drinking coffee or other substances with caffeine after dinner	0.723	0.602	-0.292	-0.393
3. Doing intense physical exercise before going to bed	0.719	0.379	0.045	0.029

4. Taking a long nap during the day	0.713	0.465	0.025	0.053
5. Going to bed and waking up always at the same hour	0.708	0.513	0.118	0.321
6. Thinking about one's engagements for the next day before falling sleep	0.715	0.600	0.043	0.392
7. Using sleep medication regularly	0.708	0.439	0.217	-0.076
8. Smoking before falling asleep	0.711	0.159	0.503	0.274
9. Diverting one's attention and relaxing before bedtime	0.718	0.370	0.015	0.373
10. Going to bed 2 h later than the habitual hour	0.720	0.320	0.134	0.003
11. Going to bed with an empty stomach	0.710	0.274	0.369	0.251
12. Using the bed for eating, calling on the phone, studying, or other non-sleeping activities	0.711	0.226	0.504	-0.291
13. Trying to fall asleep without having a sleep sensation	0.712	0.422	0.206	0.012
14. Studying or working intensely until late night	0.713	0.029	0.681	0.015
15. Getting up when it is difficult to fall asleep	0.714	0.253	0.340	0.141
16. Going to bed 2 h earlier than the habitual hour	0.716	0.095	0.558	-0.002
17. Going to bed immediately after eating	0.699	0.566	0.260	-0.186
18. Being worried about the impossibility of getting enough sleep	0.707	0.468	0.259	-0.016
19. Sleeping in a quiet and dark room	0.711	0.452	0.134	0.210
20. Recovering lost sleep by sleeping for a long time	0.721	0.193	0.376	-0.463
Total sample	0.725	8.64 ± 0.14	4.74 ± 0.09	2.26 ± 0.05
Group				
SUD	0.820	8.59 ± 2.45	4.66 ± 1.52	2,26 ± 0.80
SUD+MDD	0.675	9.8 ± 1.32	5.2 ± 1.21	2.25 ± 0.69
SUD+SZ	0.729	8.21 ± 2.49	4.52 ± 1.23	2.17 ± 0.74

As we observed in table 18, the components loading were low in some items, and dimensions items did not match to original Spanish scale (Adan et al., 2006). Therefore, by eliminating seven items (item1, item2, item10, item15, item16, item18, item20) we reached to optimal factor analyses. The mean score for the total reduced SBS was 10.39 ± 2.40; (range 0-13) in the total sample, suggesting a biased distribution to higher scores (correct beliefs) ($Z = 0.214$; $p<0.001$). The mean score of the SUD group was 10.24 ± 2.86 showing a biased distribution to higher scores ($Z = 0.231$; $p<0.001$). For the SUD+MDD group, the score was 10.96 ± 1.45 and for the SUD + SZ the score was 9.92 ± 2.58, also in both cases (SUD + MDD: $Z = 0.205$; $p<0.001$ and SUD+SZ: $Z = 0.195$; $p<0.001$) indicating a biased distribution to higher scores. In the total sample, the mean score for Sleep-incompatible behaviors was 4.74 ± 1.40; (range 0-6), for Sleep-wake-cycle behaviors was 3.18 ± 0.99; (range 0-4), and for Thoughts and attitudes to sleep was 2.47 ± 0.78; (range 0-3), suggesting

a biased distribution to higher scores (correct beliefs) in all three cases: Sleep-incompatible behaviors (Z = 0.221; p<0.001), Sleep-wake-cycle behaviors (Z = 0.261; p<0.001) and Thoughts and attitudes to sleep (Z = 0.372; p<0.001).

The screen plot of the exploratory factor analysis of the SBS using the extraction method of principal components indicated that three dimensions with an eigenvalue >1.1 should be retained, accounting for 39.8% of the total sample variance (F1 = 15.1%, F2 = 12.9%, F3 = 11.8%). This reduced proposal of the SBS provides similar internal reliability for total score (α = 0.710) and dimensions (Sleep-incompatible behaviors: 0.594; Sleep-wake-cycle behaviors: α = 0.484 and Thoughts and attitudes to sleep: α = 0.546) to the original scale; in addition explained a higher percentage of variance in all cases with respect to the psychometric properties of the original scale. The orthogonal Varimax rotation final solution is presented in Table 19, where all the items are grouped in the three factors. The first factor, "Sleep-incompatible behaviors", was composed by six items (item 7, item 8, item 11, item 12, item 14, item 17); the second factor, "Sleep-wake-cycle behaviors", included four items (item 3, item 4, item 5, item 19) and the third factor, "Thoughts and attitudes to sleep", was composed by three items (item 6, item 9 and item 13). All the three dimensions, Sleep-incompatible behaviors ($\rho = 0.798$, p<0.01), Sleep-wake-cycle behaviors ($\rho = 0.668$, p<0.01) and Thoughts and attitudes to sleep ($\rho = 0.583$, p<0.01) correlate significantly with the total score of the SBS.

Table 19. Internal reliability (Cronbach's α) for all 13 items of the scale (if one item is deleted) and principal component analysis: Varimax rotated final solution where loadings in bold identify the factor to which the item was assigned. Mean scores and standard deviation in the total sample and the three groups of SUD (substance use disorder), SUD+MDD (substance use disorder comorbid major depressive disorder) and SUD+SZ (substance use disorder comorbid schizophrenia) patients.

Item	α	F1	F2	F3
3. Doing intense physical exercise before going to bed	0.689	0.123	**0.583**	-0.024
4. Taking a long nap during the day	0.683	0.034	**0.695**	0.071
5. Going to bed and waking up always at the same hour	0.668	0.085	**0.530**	0.445
6. Thinking about one's engagements for the next day before falling sleep	0.677	0.032	0.140	**0.722**
7. Using sleep medication regularly	0.672	**0.578**	-0.045	0.286

8. Smoking before falling asleep	0.673	**0.534**	0.007	0.238
9. Diverting one's attention and relaxing before bedtime	0.688	0.045	-0.065	**0.691**
11. Going to bed with an empty stomach	0.679	**0.545**	0.080	0.048
12. Using the bed for eating, calling on the phone, studying, or other non-sleeping activities	0.683	**0.597**	0.125	-0.088
13. Trying to fall asleep without having a sleep sensation	0.674	0.314	0.112	**0.428**
14. Studying or working intensely until late night	0.679	**0.570**	0.159	-0.051
17. Going to bed immediately after eating	0.666	**0.471**	0.269	0.196
19. Sleeping in a quiet and dark room	0.676	0.159	**0.596**	0.142
Total sample	0.710	4.74 ± 1.40	3.18 ± 0.99	2.47 ± 0.78
Group				
SUD	0.803	4.64 ± 1.57	3.10 ± 1.08	2.51 ± 0.76
SUD+MDD	0.635	5.1 ± 1 .09	3.28 ± 0.82	2.67 ± 0.57
SUD+SZ	0.701	4.55 ± 1.46	3.15 ± 1.09	2.23 ± 0.93

Despite the poor psychometric properties results of the factorial structure of the original SBS in the total sample of patients, we now present the results of the analyses for both the total items of the scale and its three dimensions as proposed in the original work in which the SBS was developed. MANCOVA analyses, with age as a covariate, showed differences among groups in the original SBS and reduced SBS dimensions including Sleep-wake-cycle behaviors, Thoughts and attitudes to sleep and Sleep-incompatible behaviors.

Results on Sleep-wake-cycle behaviors and Sleep-incompatible behaviors showed that SUD+MDD patients had better scores in both dimensions compared with SUD+SZ ($p<0.05$) but no difference was identified with the SUD group (see Table 20). We did not find any differences in Thoughts and attitudes to sleep among groups. For the total score of SBS the SUD+MDD group showed a better score than the SUD+SZ group ($p<0.01$) but no difference with the SUD group was noticed. In other words, both of SUD+MDD and SUD groups got the best scores in beliefs of sleep in comparison to SUD+SZ group. On the other hand, the second MANCOVA analysis considering age and age of onset of SUD as covariates eliminated the differences in Sleep-wake-cycle behaviors appreciated previously. However, the differences in Sleep-incompatible behaviors among groups were also observed in the second analysis (see Table 20). Considering the total score of SBS, SUD+MDD patients obtained better scores than SUD+SZ patients ($p<0.05$) but no difference with the SUD group was noticed.

In the reduced SBS, results on Thought and attitude to sleep showed that SUD+SZ patients showed worse scores compared with SUD ($p<0.05$) and SUD+MDD ($p<0.05$) groups but no significant differences were identified between SUD and SUD+MDD groups (see Table 21). In other words, the SUD+SZ group showed the worst scores in Thought and attitude to sleep among the three groups of patients. Results for the total score of reduced SBS, was the same as original. The SUD+MDD group showed a better score than the SUD+SZ group ($p<0.01$) but no difference with the SUD group was noticed. We did not find any differences in two other dimensions among groups. On the other hand, the second MANCOVA analysis considering age and age of onset of SUD as covariates showed the same results as the first MANCOVA (see Table 21). Means of both total scores and dimensions of original and reduced SBS in the three groups of SUD, SUD+MDD and SUD+SZ are shown in Figures 11,12,13, and 14 respectively.

Table 20. Original SBS total score and the dimensions of the three groups of SUD (substance use disorder), SUD+MDD (substance use disorder comorbid major depressive disorder) and SUD+SZ (substance use disorder comorbid schizophrenia) patients. Mean scores, standard deviation with F and partial eta square (η_p^2) tests (MANCOVA results).

				Age as covariate		Age and age of onset of SUD as covariates	
Original SBS	SUD	SUD+MDD	SUD+SZ	$F_{(2,234)}$	η_p^2	$F_{(2,233)}$	η_p^2
Total SBS score	15.52 ± 3.93	16.46 ± 1.97	14.90 ± 3.52	4.755**	0.039	4.227*	0.035
Sleep-wake-cycle behavior	8.59 ± 2.45	9.08 ± 1.32	8.21 ± 2.49	3.359*	0.028	2.763	0.023
Sleep-incompatible behaviors	4.66 ± 1.52	5.02 ± 1.21	4.52 ± 1.23	3.242*	0.027	3.347*	0.028
Thoughts and attitudes to sleep	2.26 ± 0.80	2.35 ± 0.69	2.17 ± 0.74	1.015	0.009	0.818	0.007

* $p<0.05$; ** $p<0.01$
SBS: Sleep beliefs scale

Table 21. Reduced SBS total score and the dimensions in the three groups of SUD (substance use disorder), SUD+MDD (substance use disorder comorbid major depressive disorder) and SUD+SZ (substance use disorder comorbid schizophrenia) patients. Mean scores, standard deviation with F and partial eta square (η_p^2) tests (MANCOVA results).

				Age as covariate		Age and age of onset of SUD as covariates	
Reduced SBS	SUD	SUD+MDD	SUD+SZ	$F_{(2,234)}$	η_p^2	$F_{(2,233)}$	η_p^2
Total SBS score	10.24 ± 2.86	10.96 ± 1.45	9.92 ± 2.58	4.058*	0.034	3.686*	0.031
Sleep-incompatible behaviors	4.64 ± 1.57	5.01 ± 1.09	4.55 ± 1.46	2.451	0.021	2.222	0.019
Sleep-wake-cycle behaviors	3.10 ± 1.08	3.28 ± 0.82	3.15 ± 1.09	0.727	0.006	0.798	0.007
Thoughts and attitudes to sleep	2.51 ± 0.76	2.67±0.57	2.23 ± 0.93	7.060**	0.057	5.880**	0.048

* p<0.05; ** p<0.01
SBS: Sleep beliefs scale

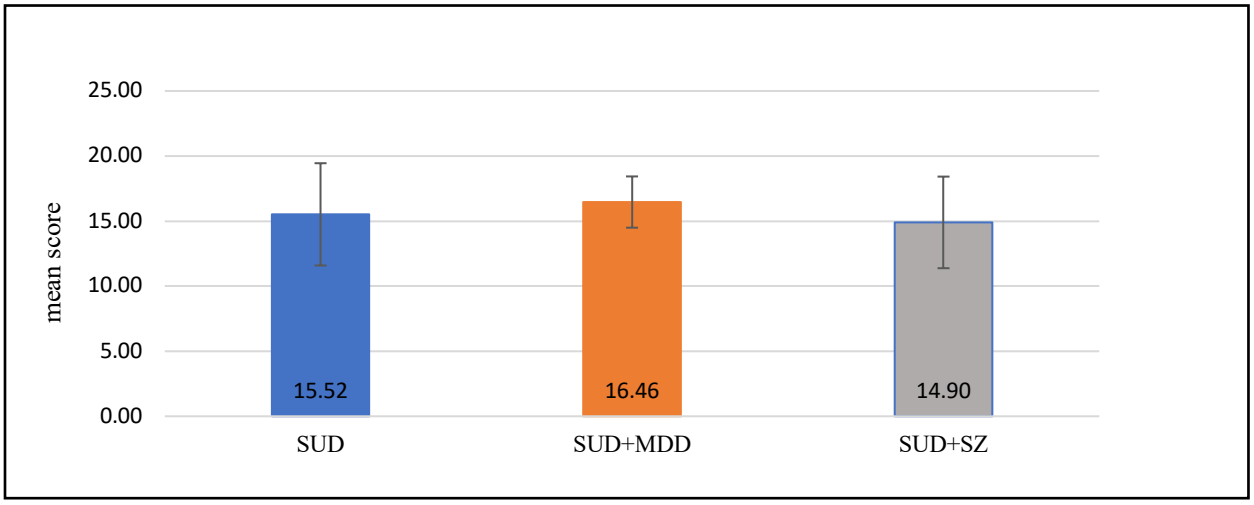


Figure 11. Mean of the total scores of original SBS (Sleep Beliefs Scale) in the groups of SUD (substance use disorder), SUD+MDD (substance use disorder comorbid major depressive disorder) and SUD+SZ (substance use disorder comorbid schizophrenia) patients.

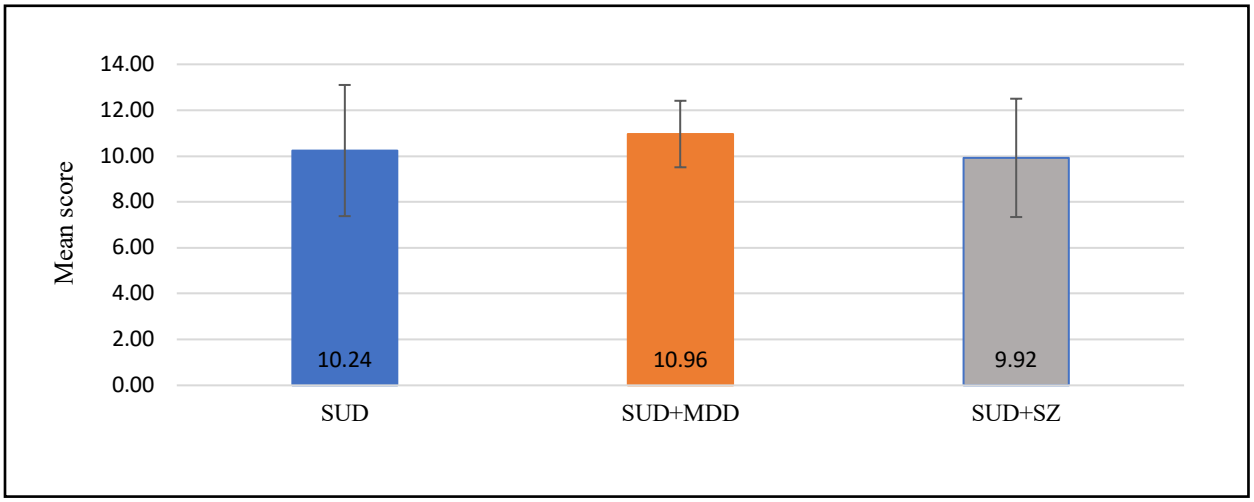


Figure 12. Mean of the total scores of reduced SBS (Sleep Beliefs Scale) in the groups of SUD (substance use disorder), SUD+MDD (substance use disorder comorbid major depressive disorder) and SUD+SZ (substance use disorder comorbid schizophrenia) patients.

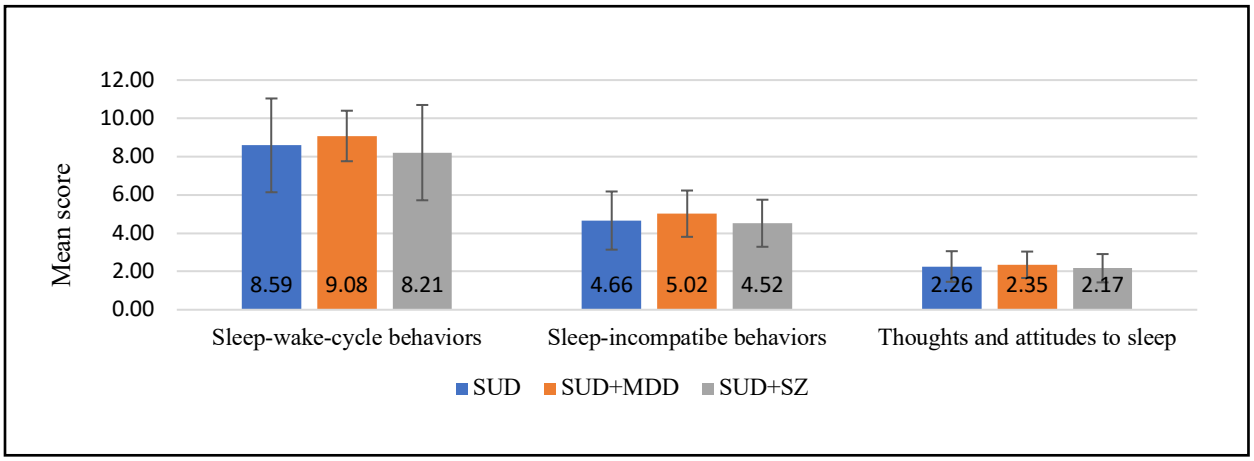


Figure 13. Mean of dimensions of the original SBS (Sleep Beliefs Scale) in the groups of SUD (substance use disorder), SUD+MDD (substance use disorder comorbid major depressive disorder) and SUD+SZ (substance use disorder comorbid schizophrenia) patients.

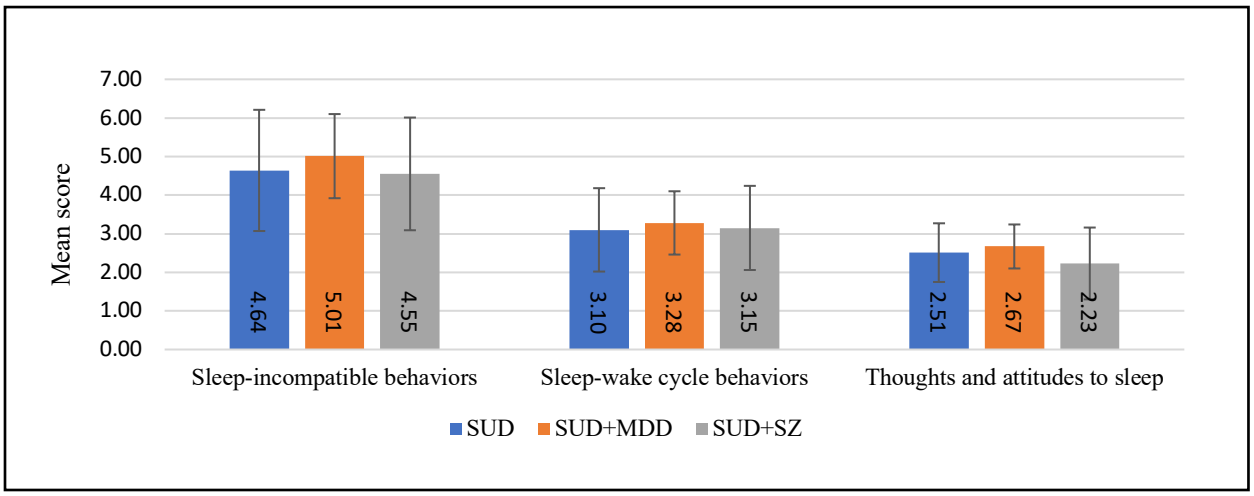


Figure 14. Mean of dimensions of the reduced SBS (Sleep Beliefs Scale) in the groups of SUD (substance use disorder), SUD+MDD (substance use disorder comorbid major depressive disorder) and SUD+SZ (substance use disorder comorbid schizophrenia) patients.

Regarding the associations between the clinical variables and the dimensions of the original SBS provided differential data depending on the group considered. In the SUD+SZ group regression analyses indicated that only the PANSS score was negatively related to Sleep-incompatible behaviors, explaining 10.2% of its variance ($F_{(1,73)} = 9.406$; $p<0.01$) (see Table 22). Meanwhile, considering the SUD+MDD group, only two variables were related to Thoughts and attitudes to sleep. Thus, scoring HAMD-17 negatively and the age of onset of SUD positively related to the Thoughts and attitudes to sleep, explaining 9.9% of its variance ($F_{(2,79)} = 4.316$; $p<0.05$). No variables were associated with Sleep-wake-cycle behaviors to sleep and total SBS score in any group.

In reduced SBS, regression analyses indicated that in the SUD+SZ group, only the number of substance use was negatively related to sleep-incompatible behaviors, explaining 4.1% of its variance ($F_{(1,73)} = 4.201$; $p<0.05$) (see Table 23). Just one variable was related to Sleep-wake-cycle behaviors in the total sample, number of substance use negatively related to the Sleep-wake- cycle behaviors, explaining 1.2% of its variance ($F_{(1.236)} = 3.925$; $p<0.05$). The number of substance use in the SUD+MDD group was negatively related to Thoughts and attitudes to sleep explaining 5.6% of its variance ($F_{(1,80)} = 5.790$; $p<0.05$). Within the SUD+SZ group, the score of PANSS was negatively related to Thoughts and attitudes to sleep explaining 9.7% of its variance in ($F_{(1,73)} =$

8.975; p<0.01). Also, in total sample, number of substance use negatively related to Thoughts and attitudes to sleep explaining 2% of its variance ($F_{(1,236)} = 5.792$; p<0.05).

Table 22. Liner regressions for original SBS (Sleep Beliefs Scale) dimensions in SUD (substance use disorder), SUD+MDD (substance use disorder comorbid major depressive disorder) and SUD+SZ (substance use disorder comorbid schizophrenia) patients.

Original SBS dimensions	Group	Adjusted R^2	IV	ß standardized	p value	Tolerance	VIF	Durbin Watson
Sleep-incompatible behaviors	SUD+SZ	0.102	PANSS	-0.338	0.003	-	-	1.829
Thoughts and attitudes to sleep	SUD+MDD	0.099	Age of onset of SUD	0.247	0.024	0.993	1.007	2.134
			HAMD-17	-0.215	0.048	0.993	1.007	

Table 23. Liner regressions for reduced SBS (Sleep Beliefs Scale) dimensions in the total sample and the three groups of SUD (substance use disorder), SUD+MDD (substance use disorder comorbid major depressive disorder) and SUD+SZ (substance use disorder comorbid schizophrenia) patients.

Reduced SBS dimensions	Group	Adjusted R^2	IV	ß standardized	p value	Durbin Watson
Sleep-incompatible behaviors	SUD+SZ	0.041	Number of substance use	-0.233	0.044	1.357
Sleep-wake-cycle behaviors	Total sample	0.012	Number of substance use	-0.128	0.048	1.877
Thoughts and attitudes to sleep	SUD+MDD	0.056	Number of substance use	-0.260	0.018	1.962
	SUD+SZ	0.097	PANSS	-0.331	0.004	1.800
	Total sample	0.020	Number of substance use	-0.155	0.017	1.726

MANCOVA analyses (see Table 24) showed that there is no interaction between CT and group in Sleep-wake-cycle behaviors. Therefore, the main effect of CT showed a significant difference in this dimension, IT (9.10 ± 1.83) reported better score compared to MTs (8.29 ± 2.01) ($p<0.05$). There was no significant difference between IT and ET (8.42 ± 2.47). In other words, ITs and ETs reported better scores in Sleep-wake-cycle behaviors compared to MTs. Moreover, there was no evidence of a significant difference in other dimensions of SBS.

In reduced SBS, MANCOVA analyses (see Table 25) indicated the same results that there is no interaction between CT and group in Sleep-wake-cycle behaviors. Therefore, the main effect of CT showed a significant difference in this dimension, IT reported better score (3.36 ± 0.85) compared to MTs (2.95 ± 1.02) ($p<0.05$) with no significant difference between IT and ET (3.14 ± 1.09). In other words, ITs and ETs reported better scores in Sleep-wake-cycle behaviors compared to MTs. Also, there was no significant difference in other dimensions of SBS.

Table 24. Statistical value (F and η_p^2) for CT (chronotype), group and their interaction on original SBS (MANCOVA results).

Original SBS	Factor	F	η_p^2
Sleep-wake-cycle behaviors	Chronotype	$F_{(2,228)} = 3.063$*	0.026
	Group	$F_{(2,228)} = 3.431$*	0.029
	Chronotype x Group	$F_{(4,228)} = 1.648$	0.028

*p<0.05
SBS: Sleep beliefs scale

Table 25. Statistical value (F and η_p^2) for CT (chronotype), group and their interaction on reduced SBS (MANCOVA results).

Reduced SBS	Factor	F	η_p^2
Sleep-wake-cycle behaviors	Chronotype	$F_{(2,228)} = 3.461$*	0.029
	Group	$F_{(2,228)} = 2.039$	0.018
	Chronotype × Group	$F_{(4,228)} = 1.530$	0.026

4.3. Quality of life (QOL)

Internal reliability for all WHOQOL-BREF dimensions was acceptable for Physical health (α = 0.730), Psychological health (α = 0.717), Social relationship (α = 0.746) and Environmental health (α = 0.736) and also considering the overall QOL (α = 0.743). Compared to the Iranian population norms, in terms of mean scores for Physical health (70.63 ± 12.38), Psychological health (62.50 ± 1 4.94), Social relationship (63.75 ± 14.81) and Environmental health (54.38 ± 14.63) (Nedjat et al., 2008), the DD groups of patients presented lower values in all dimensions. In this regard, the Physical health of SUD (t_{91} = -8.340, p<0.001), SUD+SZ (t_{93} = -16.040, p<0.001) and SUD+MDD (t_{96} = -15.160, p<0.001) patients got scores lower than norm respectively. Also the same in the Psychological health SUD (t_{95} = -4.691, p<0.001), SUD+SZ (t_{95} = -8.790, p<0.001) and SUD+MDD (t_{102} = -11.230, p<0.001) groups scored lower than norm. The SUD (t_{92} =-2.122, p<0.05), SUD+MDD (t_{97} = -7.220, p<0.001) and SUD+SZ (t_{86} = -9.210, p<0.001) groups in the Social relationship scored lower than norm respectively. Although, in the Environmental health SUD group was similar to the norm, SUD+MDD (t_{109} = -5.330, p<0.001) and SUD+SZ (t_{95} = -6.471, p<0.001) reported lower scores.

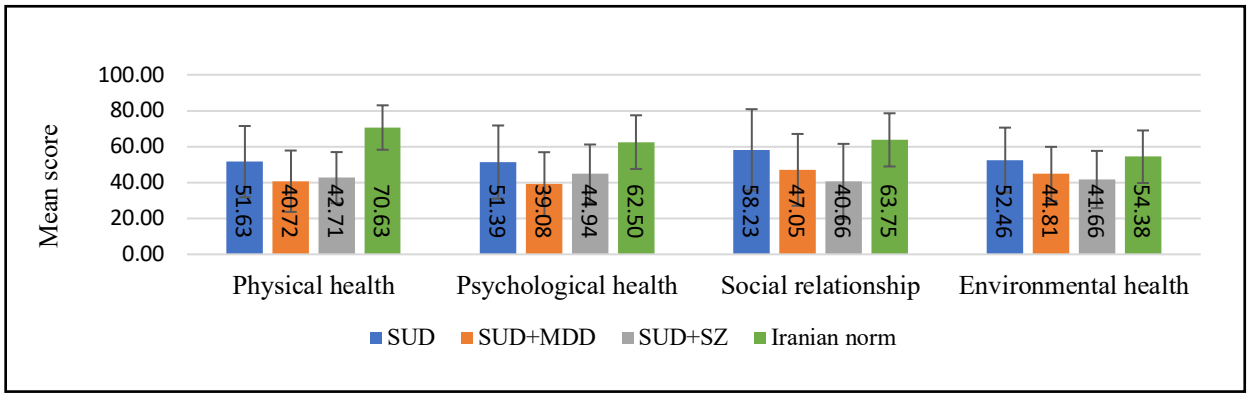


Figure 15. Mean differences of WHOQOL-BREF (World Health Organization's Quality of Life) dimensions in the three groups of SUD (substance use disorder), SUD+MDD (substance use disorder comorbid major depressive disorder) and SUD+SZ (substance use disorder comorbid schizophrenia) patients and the Iranian population norms.

MANCOVA analysis using age as a covariate showed differences among groups in the QOL and its four dimensions (see Table 26). Results on Physical health showed that SUD patients presented the highest scores compared with both SUD+MDD ($p<0.001$) and SUD+SZ patients ($p<0.01$). Scores on Psychological health were higher among patients in the SUD group compared with the SUD+MDD and SUD+SZ groups ($p<0.001$). Results regarding Social relationship and Environmental health showed that SUD patients presented the highest scores compared with SUD+MDD and SUD+SZ patients ($p<0.001$, in both cases). For the overall QOL, SUD patients also presented the highest scores compared to SUD+SZ and SUD+MDD patients ($p<0.01$, in both cases). On the other hand, the second MANCOVA analysis considering age and age of onset of SUD as covariates showed the same result as previous.

Table 26. QOL (quality of life) results in the three groups of SUD (substance use disorder), SUD+MDD (substance use disorder comorbid major depressive disorder) and SUD+SZ (substance use disorder comorbid schizophrenia) patients. Mean scores, standard deviation, F and partial eta square (η_p^2) tests (MANCOVA results).

				Age as covariate		Age and age of onset of SUD as covariates	
WHOQOL-BREF	SUD	SUD+MDD	SUD+SZ	$F_{(2,234)}$	η_p^2	$F_{(2,233)}$	η_p^2
Overall QOL	51.70 ± 24.10	44.05 ± 19.86	41.50 ± 20.46	5.406**	0.044	5.202**	0.043
Physical health	51.63 ± 19.85	40.72 ± 17.08	42.71 ± 14.23	9.683***	0.076	9.742***	0.077
Psychological health	51.38 ± 20.38	39.07 ± 17.80	44.94 ± 16.22	9.453***	0.075	10.111***	0.080
Social relationship	58.23 ± 22.61	47.05 ± 20.00	40.66 ± 20.86	13.954***	0.107	13.119***	0.101
Environmental health	52.46 ± 18.11	44.81 ± 15.06	41.66 ± 1.84	9.460***	0.075	9.143***	0.073

** $p<0.01$; *** $p<0.001$
WHOQOL: World health organization's quality of life

Multiple regression analysis of WHOQOL-BREF and its dimensions scales related to clinical variables are presented in Table 27. For the SUD+SZ group, both previous suicide attempts and SJL were negatively related to Physical health, explaining 10.3% of the variance in this dimension ($F_{(2,72)} = 5.226$; $p<0.01$). No variables were associated with Physical health in the SUD group. The score of PANSS in the SUD+SZ group was negatively related to Psychological health explaining 5.5% of its variance ($F_{(1,73)} = 5.275$; $p<0.05$).

Within the SUD+MDD group, the SJL with explaining 4.1% of its variance ($F_{(1,80)}$ = 4.440; $p<0.05$) and HAMD-17 with explaining 6.5% of its variance in ($F_{(1,80)}$ = 6.675; $p<0.05$) were negatively related to psychological health. No variables were associated with Psychological health in the SUD group. In the SUD+SZ group, previous suicide attempts and PANSS were negatively related to Social relationship, explaining 16.4% of its variance ($F_{(1,72)}$ = 8.280; $p<0.01$). No variables were associated with the Social relationship in the SUD and SUD+MDD groups. In the SUD+SZ group, SJL was negatively related to overall QOL, explaining 8.2% of its variance ($F_{(1,73)}$ = 7.600; $p<0.01$). In the total sample, number of substance use was negatively related to overall QOL, explaining 1.3% of its variance ($F_{(1,236)}$ = 4.196; $p<0.05$). No variables were associated with overall QOL in SUD and SUD+MDD groups nor with Environmental health in any group.

Table 27. Multiple liner regressions for WHOQOL-BREF (World Health Organization's Quality of Life) in the total sample and the three groups of SUD (substance use disorder), SUD+MDD (substance use disorder comorbid major depressive disorder) and SUD+SZ (substance use disorder comorbid schizophrenia) patients.

WHOQOL-BREF dimensions	Group	Adjusted R^2	IV	ß standardized	p value	Tolerance	VIF	Durbin Watson
Physical health	SUD+SZ	0.103	Previous suicide attempts	-0.258	0.022	0.999	1.001	1.955
			SJL	-0.240	0.033	0.999	1.001	
	SUD+MDD	0.041	SJL	-0.229	0.038			1.578
Psychological health	SUD+SZ	0.055	PANSS	-0.260	0.025			1.948
	SUD+MDD	0.065	HAMD-17	-0.278	0.012			1.677
Social relationship	SUD+SZ	0.164	Previous suicide attempts	-0.341	0.002	0.974	1.026	1.531
			PANSS	-0.217	0.048	0.974	1.026	
Overall QOL	SUD+SZ	0.082	SJL	-0.307	0.007			2.332
	Total sample	0.013	Number of substance use	-0.277	0.042			1.727

We were used MANCOVA analysis to see the differences between levels of PSQI dimensions on QOL dimensions. This analysis showed no interaction between sleep quality and groups in Physical health, Psychological health, and Environmental health. Therefore, the main effect of sleep quality appears significant in Physical health (see Table 28); the patients who reported very good or fairly good sleep quality had higher Physical health compared to fairly bad and very bad ones ($p<0.05$, in both cases) (see Table 29). Also, there was a significant difference between sleep

quality levels in Psychological health. The patients who reported very good or fairly good sleep quality had higher psychological Health compared to fairly bad and very bad ones ($p<0.05$), in both cases). Also, a significant difference was observed between sleep quality levels in Environmental health. The patients who reported very good or fairly good sleep quality had higher Environmental health compared to fairly bad and very bad ones ($p<0.05$, in both cases). There was no evidence of significant difference in social relationship, the other dimension of WHOQOL.

Table 28. Statistical value (F and η_p^2) for sleep quality, group and their interaction on QOL (Quality of Life) (MANCOVA results).

WHOQOL-BREF	Factor	F	η_p^2
Physical health	Sleep quality	$F_{(3,225)}$ =9.850***	0.116
	Group	$F_{(2,225)}$ =6.892**	0.058
	Sleep quality × Group	$F_{(6,225)}$ =1.566	0.040
Psychological health	Sleep quality	$F_{(3,225)}$ =6.509***	0.080
	Group	$F_{(2,225)}$ =4.040*	0.035
	Sleep quality × Group	$F_{(6,225)}$ =2.018	0.051
Environmental health	Sleep quality	$F_{(3,225)}$ =4.471**	0.056
	Group	$F_{(2,225)}$ =8.379***	0.069
	Sleep quality × Group	$F_{(6,225)}$ =1.779	0.045

* p<0.05; ** p<0.01; *** p<0.001
WHOQOL: World health organization's quality of life

Table 29. The QOL (Quality of Life) dimensions according to sleep quality. Mean scores and standard deviation.

WHOQOL-BREF	Sleep quality			
	Very good	Fairly good	Fairly bad	Very bad
Physical health	52.14 ± 18.47	48.98 ± 16.54	39.11 ± 16.84	35.12 ± 17.12
Psychological health	51.11 ± 19.63	48.81 ± 18.17	39.38 ± 17.56	36.67 ± 18.36
Environmental health	52.29 ± 20.37	48.36 ± 16.98	43.60 ± 14.41	38.96 ± 15.39

WHOQOL: World health organization's quality of life

MANCOVA analyses showed an interaction between sleep latency and group in Physical health (see Table 30). A significant difference was observed between sleep latency levels in Physical health in the SUD+MDD group, the patients who reported more than 60 minutes of sleep latency had lower Physical health compared to the other three latency levels ($p<0.05$) (see Table 31). There was no interaction between sleep latency levels and group in terms of Psychological health. In the

Psychological health, the significant difference among sleep latency levels was observed by the main effect. In this regard, the patients with shorted sleep latency than 15 minutes had higher Psychological health compared to those with 16-30 minutes and more than 60 minutes of sleep latency ($p<0.05$, in both cases). The patient who reported 31-60 minutes of sleep latency had higher Psychological health rather than those with 16-30 minutes and more than 60 minutes of sleep latency ($p<0.05$, in both cases). In other words, the patients with shorter latency reported higher Psychological health. There was no evidence of a significant difference in other dimensions of WHOQOL. Correlation between scores of QOL and PSQI using the Pearson test also revealed a negative correlation between them ($\rho = -0.170$, $p<0.01$). In the total sample, suggesting that patients who reported better quality of sleep had a better QOL. The correlation performed for each clinical group no did not provide differences in any of them. Besides, MANCOVA analysis adding CTs as a factor revealed no significant difference for CTs nor for their interaction with group in QOL.

Table 30. Statistical value (F and η_p^2) for sleep latency, group and their interaction on QOL (Quality of Life) (MANCOVA results).

WHOQOL-BREF	Factor	F	η_p^2
Physical health	Sleep latency	$F_{(3,225)}$ =1.095	0.014
	Group	$F_{(2,225)}$ =9.077***	0.075
	Sleep latency × Group	$F_{(6,225)}$ =2.896*	0.072
Psychological health	Sleep latency	$F_{(3,225)}$ =2.761*	0.036
	Group	$F_{(2,225)}$ =7.467**	0.062
	Sleep latency × Group	$F_{(6,225)}$ =2.121	0.054

* p<0.05; ** p<0.01; *** p<0.001
WHOQOL: World health organization's quality of life

Table 31. The QOL (Quality of life) dimensions according to sleep latency levels. Mean scores, standard deviation, F and partial eta square (η_p^2).

WHOQOL-BREF	Group	Sleep latency					
		lower than 15 minutes	16-30 minutes	31-60 minutes	more than 60 minutes	F	η_p^2
Physical health	Total sample	20.54 ±5 .26	19.00 ± 4.21	19.81 ± 4.49	16.78 ± 5.73		-
	SUD	22.54 ± 5 .45	18.44 ± 5.56	22.4 ± 5.08	24.33 ± 5.03	$F_{(3,76)}$ =2.679	0.096
	SUD+MDD	18.68 ± 5.61	19.74 ± 4.09	18.26 ± 4.45	13.60 ± 3.10	$F_{(3,77)}$ =4.006*	0.135
	SUD+SZ	19.3 ± 4.11	18.38 ± 3.06	19.29 ± 4.70	18.60 ± 5.77	$F_{(3,70)}$ =0.339	0.014
Psychological health	Total sample	17.54 ± 4.48	15.9 ± 3.36	17.70 ± 5.18	14.44 ± 4.18	-	-

* p<0.05
WHOQOL: World health organization's quality of life

5. DISCUSSION

The current study sought to explore the characteristics and possible differences of sociodemographic and clinical state in SUD, SUD+SZ and SUD+MDD Iranian patients under treatment, as well as their circadian functioning (SJL, CT, quality of sleep and sleep beliefs), and QOL. We also aimed to compare data from our sample in rMEQ and QOL with population norms and identify clinical correlates of sleep and circadian rhythmicity characteristics in SUD, SUD+SZ and SUD+MDD patients.

5.1. Sociodemographic and clinical characteristics

Based on the results of this study, the sociodemographic characteristics of the patients was similar to several previous studies in Iran and other countries. In line with one Iranian study (Habibisaravi et al., 2015) and other countries (Talamo et al., 2006; Wobrock et al., 2013; Patel et al., 2016; Laskemoen et al., 2019; Marquez-Arrico et al., 2019a) patients in SUD+SZ group were more younger and majority of them were single (Stompe et al., 2018; Bouri et al., 2020) than SUD ones. These results are in contrary with a previous study (Benaiges et al., 2012) in which only composed men, the possible reasons for the differences in the results could come from the different type and rate of substance use as cocaine, cannabis and alcohol and different social and religious values in comparison with our study. In line with previous works, we did not find any significant differences in socio-economic levels and employment status among the groups (Benaiges et al., 2012; Antúnez et al., 2016).

We found that the DD patients (SUD+MDD and SUD+SZ) have lower levels of education with a higher rate of illiterate while SUD ones presented higher education levels (Wobrock et al., 2013; Mortazavi et al., 2015; Laskemoen et al., 2019). It should be mentioned here that our comparison is limited to patient groups and not to the data of the normal population in Iran-Shiraz. This result is contradictory with those of other studies on SUD with psychotic spectrum disorder patients, which reported more rate of illiteracy in SUD patients in urban areas in India (Aich, 2004) or Iran-Sari (Habibisaravi et al., 2015) or unlike with other studies that were not observed any significant differences in marital status and education levels of SUD and DD patients (Swartz et al., 2006;

Benaiges et al., 2012; Aras et al., 2013; Uludag & Gülec, 2016). The reasons that can differentiate the results are the type of gender population as well as conducted geographical areas and age of onset of SUD. In Iranian society, higher education is an effective feature, so in the normal population, people have a greater tendency toward higher education. In the present study, it can be concluded that SUD patients show a greater tendency to continue their education due to less mental and psychological conflicts than DD patients. In other words, since DD patients clinically suffering more severe illness than the patients with only one disorder (Margolese et al., 2006; Jones & McCance-Katz, 2019) which also endure lower social support consultation (Marquez-Arrico et al., 2015; Adan et al., 2017b; Marquez-Arrico et al., 2019b) can be an obstacle to the development. Another possible reason is the age of initiation of substance use, in adolescence and early youth. Although the diagnosis of SUD is usually made a few years later (it is estimated to be a decade), the consumption of patients may have affected the education and access to the world of work of the patients. Therefore, it may lead to reluctancy to advance in social opportunities such as work promotions and achievement to higher educational levels. From another point of view, cultural differences in each society, such as differences in financial and social levels and personality traits, can lead to different results in sociodemographic variables. Thus, it is recommended to conduct intercultural research to account for deeply in these data in the future, especially among DDs and their possible differences according to the comorbid disorder and regarding the diagnosis of only SUD.

In this study, the SUD group reported more law and legal problems than DD patients. The greater presence of problems in SUD can be related to the greater impulsivity in them (Perry & Carroll, 2008; Verdejo-García et al., 2008; Shochat et al., 2014; Adan et al., 2017d; Daigre et al., 2017), while the DD patients are found in practically all cases with treatment for the comorbid disorder, very commonly with sedative and/or anxiolytic actions that can minimize problem behaviors. Thus, requesting better social connections in SUD patients (Zarrabi et al., 2009; Benaiges et al., 2012) may lead to a higher report of legal and law problems in the face of social conditions. On the other hand, regarding the characteristics of the depression and psychotic spectrum disorders (Hasin & Grant, 2004; APA, 2013), being more alone or being in small groups and feeling of loneliness (Van Den Brink et al., 2018; Marquez-Arrico et al., 2019a), as well as lack of energy to find substances (Kalechstein et al., 2002; Leventhal et al., 2008) can also be explanatory factors to have less illegal behavior in the DD groups. However, other researchers have shown conflicting

results regarding social problems and reported more delinquent behaviors in DD patients than those without comorbidity (NIDA, 2007; Verdejo-García, 2008; Suokas et al., 2010; Aras et al., 2013; Torrens et al., 2017). One possible reason could be the lack of compatible strategies to cope with problems in DDs in comparison with patients with only SUD diagnosis (Adan et al., 2017b; Marquez-Arrico et al., 2019a). Since DD patients suffer more problems in skills of problem-solving (Adan et al., 2017c), social abilities with cognitive deficits (Kerner, 2015; Wobrock et al., 2013), and more self-blaming and guilt feeling (Marquez-Arrico et al., 2019a), several strategies have been proposed to prevent delinquent behaviors and high consumption of drugs in these patients. Intervention programs (Subodh et al., 2018) such as emotional self-control skills and managing negative emotions can improve their effectiveness (Adan et al., 2017d). This purpose can be realized through more accurate personality traits and neurocognitive assessment to investigate the interaction between individual functioning and behaviors of SUD and DD patients. Hence, further research in this area could pave the road for a better understanding of the issue in SUD patients with/without comorbidity.

Although we were unable to record clinical data of abstinence time/period of substance regarding lack of access and data, previous studies (Marquez et al., 2019a; Río-Martínez et al., 2020) have not find any association between this variable and clinical features related to diagnosis groups. However, another study (Adan et al., 2017c) reported that although DD and SZ patients did not show differences in length of abstinence that could be a modulating factor the executive function of SZ patients. Moreover, SPs have been more reported in smokers compared to the control group but disappeared during abstinence time (Bender et al., 2020). In this line, a study (Brown et al., 2010) reported that after a 12-week exercise and aerobic sessions, a significant increase in abstinence from substance use and alcohol appeared and patients with more problems could experience more difficulties in achieving abstinence (Daigre et al., 2017). Summarizing, different researches results highlight the importance of biological and behavioral aspects that influence months of abstinence. Therefore, more research is recommended to achieve a better understanding of this line of undoubted value to better understand the multiple factors that influence adherence to treatment.

Consistent with previous findings, DD patients showed higher rates of medical disorder comorbidity (Dickey et al., 2002; Salloum et al., 2004; Drake, 2007; Rodriguez-Jimenez et al.,

2008; Lubman et al., 2010; Casares-López et al., 2011; Sara et al., 2014; Marquez-Arrico et al., 2019a; Levola et al., 2020) and more suicide attempts (Brunette et al., 2006; Benaiges et al., 2012; Østergaard et al., 2017; Marquez-Arrico et al., 2019a; Río-Martínez et al., 2020). This was especially evident in the case of SUD+MDD patients, as several studies have obtained (Johnson & Zlotnick, 2012; Adan et al., 2017b). Consistent with another study (Benaiges et al., 2012), we did not find differences among groups in psychiatric and SUD family history; however, a higher number of first-degree relatives both with SUD and psychiatric disorders was found in another study (Adan et al., 2017c). This study showed a greater rate of alcohol in DD patients and since the sale and free consumption of alcohol prohibited in Iran (Habibisaravi et al., 2015; Amin-Esmaeili et al., 2017; Taghinejad et al., 2020), unlike other countries, it can be an explanatory reason for the difference in results.

The age of onset of SUD is younger in DD patients compared to SUD patients, according to several studies (Leadbeater et al., 2019; Marquez-Arrico et al., 2019a), this data is especially marked in SUD+SZ (Barnes et al., 2006; Marquez-Arrico et al., 2019a). SUD+MDDs reported the oldest age of onset of SUD of the three groups. In this sense, previous studies explained the later age of onset of SUD in MDDs restricts the duration of activities done as a result of arranging addiction-related behaviors (Kalechstein et al., 2002; Conrod et al., 2016; Marquez-Arrico et al., 2019a). The SUD+SZ group in our study reported the higher number of substance use (Ghaffari Nejad et al., 2009; Adan et al., 2017c; Bouri et al., 2020) than two other groups and more polydrug pattern than SUD+MDD patients. This finding is contrary to previous work in Iran (Sepehrmanesh et al., 2014) that found polydrug use is more frequent in both DD groups. The lower polydrug use in the SUD+MDD group in our finding, also with respect to SUD, can be related by anhedonia feeling, the loss of interest or pleasure in activities previously enjoyed, or psychomotor retardation. In this regard, they do not have the energy to find substances or may not have experienced symptoms that motivate people to use substances (Kalechstein et al., 2002; Leventhal et al., 2008). It seems that these observations are independent of the culture category, although we must be limited only to men this conclusion since research with women can produce different results.

Consistent with similar studies (Uludag & Gülec, 2016; Laskemoen et al., 2019), in the current research, DD patients reported more personal psychiatric history than SUD ones. Further, we confirm that in the SUD+MDD group there was a higher proportion of Adjustment disorder

(Mitchell et al., 2011), of anxiety or General anxiety disorder (Kranzler & Rosenthal, 2003; Gual, 2007; Hartley et al., 2012: Mortazavi et al., 2015) and of course depressive symptoms (Howland et al., 2009; Turna et al., 2019) compared to SUD group. This highlights the importance of more depth interventions in the future, focused on secondary psychiatric symptoms to achieve better adherence and therapeutic results for these DD patients. Various reasons have been mentioned for the higher prevalence of additional mental disorders in DD than the single ones. One reason could be that the DD patients are more prone to withdraw treatment and follow up sessions, both SUD+SZ (Schmidt et al., 2011) and SUD+MDD (Daigre et al., 2019). Accordingly, they show slower improvement in the treatment process (Horsfall et al., 2009) such that even with the follow-up sessions, DD patients are especially at risk of relapse and recurrence (Xie et al., 2005; 2010; Searby et al., 2020). As a result, many of these patients turn to use substances as self-medication (Wadsworth et al., 2005; Keller et al., 2007; Bouri et al., 2020) trying to reduce the severity of their illness (Norman & Malla, 2002), side effects of medication or stress (Kalman et al., 2005). This can be especially noticeable with the presence of symptoms of comorbid disorders in our DD patients, who may want to manage their negative-positive symptoms (SUD+SZ) and depressive symptoms (SUD+MDD) in this way (Mueser et al., 1998; Talamo et al., 2006; Lubman et al., 2010; Teesson & Proudfoot, 2013; Bouri et al., 2020). In several other studies, some factors such as non-pharmacological, loss of faith in the treatment and higher insight to the illness (Hawton et al., 2005; Hor & Taylor, 2010; Boyer et al., 2012; Adan et al., 2017c; Ehrminger et al., 2019) followed by more depression feeling (Lincoln et al., 2007), especially in SUD+SZ patients, have been mentioned as possible reasons of long-term illness. These factors are accompanied by several exacerbations with the possibility of suffering more mental illnesses and reducing the time searching treatment after the onset of psychosis (Norman & Malla, 2002; Aras et al., 2013).

Although our study was a cross-sectional research and we were would not be able to include the therapeutic aspects in the research, higher education levels have pointed as a factor that can help the SUD patients to avoid exacerbating their illness regarding treatment sessions (Christensen et al., 2017; Daigre et al., 2019). These results are in line with our work about higher education levels and a lower rate of medical and mental disorders in SUD patients. Other results emphasize that integrating treatment strategies both for DDs or SUD alone are long-term goals that need to be considered (Marquez-Arrico et al., 2019b; Zhou et al., 2019). Moreover, timely engagement in a person's illness while helping to reduce SUD has a better chance of recovery and can reduce

relapse rates with improvements in the treatment process (Foulds et al., 2015; Fantuzzi & Mezzina, 2020). Previous results also show that socioeconomically vulnerable populations are more prone to develop addiction and to relapses of treatment, suggesting the requirement to implement approaches that improve the socioeconomic situation such as having a stable habitation, employment, and income in recovered SUD patients (Lee et al., 2018; 2020). Thus, it is recommended to conduct future studies, especially longitudinal, to assess whether to integrate into therapeutic management these aspects provide more effective treatment methods to support patients in the adherence to treatment.

In terms of substance consumption, in line with previous findings, our results indicated that in Iran, opium is in the first and highest rank of substance use among the SUD patients (Mokri et al., 2002; Shekarizadeh et al., 2012; Jafarikhounigh et al., 2014; Ghoreishi et al., 2017; Massah et al., 2018; Roshanpajouh et al., 2020; Taghinejad et al., 2020). This result is contrary to previous studies (Hosseini et al., 2008; Sepehrmanesh et al., 2014; Mortazavi et al., 2015) that opium use is the first substance use among DD patients in Iran. Also, our data indicated that crystal use is the second substance after opium use by the SUD group (Ghoreishi et al., 2017). In contrary to previous Iranian research (Ghaffari Nejad et al., 2009), although heroin use was more frequent in DD patients especially in the SUD+SZ group, it was no different from the SUD patients. As there is little known about the prevalence of SUD comorbid severe mental illness in Iran, future research should consider more precisely the related substances in both SUD+SZ and SUD+MDD patients. Although we did not find any significant difference in nicotine use among the studied groups, and it was found that the Iranian population mostly use nicotine (Habibisaravi et al., 2015; Saberi et al., 2018) and opium, in this order (Bahdani & Habrani, 2011; Sarrami et al., 2013), a different pattern from that group of patients who have developed SUD with or without comorbidity. In contrast to Iranian investigations, European ones reported more nicotine, alcohol and cannabis use (Gobel et al. 2016; Manthey et al., 2016; Peacock et al., 2019; Pillon et al., 2019) as well as a higher prevalence of alcohol and nicotine consumption (Adan et al., 2017c; Zhou et al., 2019) and alcohol and cocaine use in DD patients (Marquez-Arrico et al., 2019a), without considering in this last case nicotine as a substance.

The differences in the type of substance use vary according to the cultural and social structure of each society (Bahdani & Habrani, 2011; Rastegari et al., 2013), and conflicting results also could

be attributed to the differences in any sample selection or availability of substance or environmental pressure to abuse substances, such as living with a drug abuser (Domino et al., 2005; Massah et al., 2018). Undoubtedly, the origin country of the data comes provides differential aspects. The lower consumption of alcohol in our patients, according to the data from most studies carried out in American and European countries, is related to religious prohibition (Clements & Cyphers, 2020; Peviani et al., 2020). Also, the high rate of opium consumption in Iran can be due to its geographical proximity to Afghanistan, which is the world's largest producer (Trovato et al., 2010; Roshanpajouh et al., 2020), while in countries far from the opium distribution route, such as Spain, consumption is minimal. This requires further research and evaluations among the Iranian population to determine the prevalence of drug use (Zamani et al., 2019) in SUD and DD patients, of course, taking to account religiosity. Several strategies have been proposed by researches to reduce the tendency to substance consumption in Iranian SUD patients that may be effective in DDs, including practicing life skills (Nazarpour et al., 2010; Barati et al., 2011; Feyzi et al., 2016), emotional support of risky individuals, and focusing of families on educating their children about the consequences of substance use (Moradi et al., 2009; Moshki et al., 2014). Since achieving better therapeutic and clinical results needs observation of the prevalence of different substance use in society, it is suggested conducting further intercultural studies on national scales. More broadly, this can lead to a better preventive approach to drug use in adolescence and early adulthood, which is established as the best treatment for substance addiction and its devastating consequences.

5.2. Circadian functioning

- **Social jet-lag and circadian typology**

Regarding the parameters of SJL, no clinical group provided data on its presence, with minimal time differences between the sleep times on weekdays and on weekends. However, the greater stability appears in the two DD groups compared to the SUD group who also contributed the later bedtime on both weekends and workdays. These results are consistent with previous works that showed SUD is a predictor of both more SJL and sleep problems (Hasler et al., 2013; Tavernier et al., 2015; Kwon et al., 2020). Although these studies did not include the DD patients it seems

substance use, regardless of the mental disorders comorbidity, can impact sleep times in clinical populations. Therefore, a strategy to regulate the levels of daily activity in the social-work schedules (Wittmann et al. 2006; Adan, 2013) of SUD with and without comorbid severe mental disorders is suggested, what may already be happening due to the treatment in our patients.. So far, very little research has been done on SJL in the clinical populations and future research should highlight this important issue with implications in the therapeutic approach. .

Despite the limited number of studies on circadian functioning and its characteristics in DD patients, our new data show that CT is different among patients with SUD, SUD+SZ and SUD+MDD. We observed that in SUD patients IT was more prevalent although lower to population norms (Rahafar et al., 2015). Meanwhile, other studies showed that the predisposition of SUD patients was either MT (Broms et al., 2011, 2012; Capella et al., 2018) or ET (Prat &Adan, 2011; Zargar et al., 2012; Hasler et al., 2013; 2015; Conroy & Arnedt, 2014; Kervran et al., 2015; Tavernier et al., 2015). In the first case, the patients were evaluated already in treatment, while in the second case they were not. In addition, other factors may be influencing the differences in CT of SUD patients can be attributed to the difference in methodology such as gender (only males or both sexes), the type of treatment (ambulatory *vs*. residential), as well as the abstinence time that if it is longer shows a better rhythmic organization with an MT pattern. Some other factors that can act as mediational between SUD and CT, although we have not studied them in the present work, are the pattern of thinking in certain times on the day (Takano & Tanno, 2011; Antypa et al., 2017), type of personality like impulsivity or novelty-seeking (Ersche et al., 2010; Adan et al., 2010a, b), and exposure to different amounts of light (Lester, 2015). All of this deserves future studies aimed at obtain a comprehensive explanatory model with applicability in the clinical management of SUD.

This is the first study in Iran that considered CTs in DD patients. According to the statistical analysis of the present study, SUD+SZ patients reported a higher percentage of ET, although this is lower than the observed in population norms. The results were the same even after controlling the possible confounding effect of age of onset of substance use. This result is in line with previous works of SZ patients compared to healthy subjects (Thomas et al., 2018) and compared with psychotic disorders (Chung et al., 2018), although they did not include SUD patients in the sample. However a tendency to MT in both SUD+MDD and SUD groups has been reported (Antúnez et

al., 2016), in our study SUD+MDD group scored almost similar to the normal population, showing a higher percentage of MT patients among groups. This results is in line with previous study that MDD remitters found more tendency to MT (Corruble et al., 2014). However, (Antypa et al., 2017) did not find any association between ET and depression, almost all other studies reported that MDD patients are more prone to be ET (Hasler et al., 2010, Abe et al., 2011; Chan et al., 2014; 2015; Müller et al., 2015; 2016a; Tonon et al., 2020). The majority of these studies have not considered dual individuals and most of them carry out evaluations coinciding with the diagnosis and compared the single mental disorders (SZ or MDD) with normal population or healthy participants and they were lacking the specific impact of severe mental disorders with DDs. So, in our case, the greater morningness could be explained by the treatment effect for SUD and also for MDD (Corruble et al., 2014; Antúnez et al., 2016; Müller et al., 2016a; Nasiri et al., 2019). Although the physiological and biological mechanism links between CR and mental disorders are unclear (Miller et al., 2015; Antúnez et al., 2016; Togo et al., 2017), our results suggest the possibility of adjusting the CT during treatment and that it should not be considered as a predictive factor in clinical features (Druiven et al., 2019; 2020). We hope that our data will encourage further study of this topic in the future, with an ideally longitudinal approach.

It has been reported that SUD individuals who start with one substance, due to brain reward system (Hamidovic & Wit, 2009; Jaehne et al., 2009; Hasler et al., 2013), later may have more tendency to consume more and to come into contact with other (Abe et al., 2011; Owens, 2014; Caviness et al., 2015; Merikanto et al., 2015). In the present study, we found an interesting association between CTs and polydrug use in SUD and SUD+SZ groups. The patients with polydrug use in the SUD group were more IT but polydrug users in both the SUD+SZ group and total sample reported more tendency toward ET. In other words, the highest rate of polydrug users were reported to be ET in interaction with the diagnoses. These findings extend previous data indicating ET individuals had more probability to use more substance (Abe et al., 2011; Prat & Adan, 2011; Hasler et al., 2013; Lemoine et al., 2013; Vollmer et al., 2014; Ghaseminejad et al., 2015; Merikanto et al., 2015; Pereira-Morales et al., 2019) and a pattern of more polydrug use (Kervran et al., 2015). Although previous studies on SUD+SZ patients did not examine the CTs, has been reported a higher rate of polydrug users (Adan et al., 2017c; Marquez-Arrico et al., 2019a). In these studies, with Spanish patients, alcohol and cocaine consumption is one of the pattern who patients reported

in a high amount in polydrug users. It is suggested that future researches focus on the type of substances, of course taking to account the CT and with respect to the culture of that community.

Since interaction between substance use and CR is mutual (Bootzin & Stevens, 2005) and there is a vicious circle between promoting/holding the substance use and comorbid mental disorders (Luca & Peris, 2020), researchers suggest exercising, better outdoors and in the morning, as an effective approach to treatment and also as a potential relapse prevention strategy for SUD patients (Adan, 2013; Wang et al., 2014; Linke & Ussher, 2015; Capella et al., 2018) which can be also be applied for polydrug users. Along with this, compliance by patients with stable schedules and oriented to the morning pattern are beneficial in both SUD and DD (Antúnez et al., 2016; Capella et al., 2018). In previous studies on the substance use in single and DD patients, there was a lack of evaluation of the type of CTs in these clinical groups, this study investigated this gap in terms of the CTs. Our work adds as a novel fact that this should be emphasized in patients who have developed a SUD with a pattern of polydrug use.

Although other studies on SUD patients showed that SJL and sleep irregular schedules are more related to ET (Tavernier et al., 2015; Danielsson et al. 2019; Arrona-Palacios et al., 2020), as it happens with the presence of depression (Merikanto et al., 2013; De Souza & Hidalgo., 2014) and related to their severity (Chelminski et al., 1999; Wong et al., 2015; Zanini et al., 2015; Feliciano et al., 2019; Tonon et al., 2020), we did not find any association among SJL, CTs and depression severity in SUD+MDD patients. However, the association between CTs and mental problems remains unknown (Miller et al., 2015; Togo et al., 2017), some studies suggest that may be as a result of maladjustment between biological timing and societal demands (Wittmann et al., 2006; Hasler et al., 2012a). In an article (Haraszti et al., 2014b), even after using covariate, ET was associated with later sleep hours in both workdays and free days. Also, a negative association between higher stress levels and more physical activity in workdays and free days was reported. This article albeit has not found any association between CTs and substance use, suggesting that stress and healthy behavior may clarify the relationship between CTs especially MT and ET. These discrepancies in results may be explained by the type of substance and sensitivity to the substance reward (Kosobud et al. 2007; Adan et al., 2017a) in clinical features.

In contrary to previous studies (Adan et al., 2017c; Whitfield-Gabrieli et al., 2018), we did not find any association between CTs and the severity of SZ. Differences in results can be caused by several factors; e.g., cultural (Roshanpagouh et al., 2020), biological and social clock distinctions (Roenneberg et al., 2003; Wittmann et al., 2006) and genetic basics (Johansson, 2003; Jankowski, 2016) but we consider essential the effects of substance use of our patients at the level of patterns of brain reactivity to the reward system (Jaehne et al., 2009; Hasler et al., 2013) and reduction in brain metabolism (Kosobud et al. 2007; Hasler et al., 2012b) in conjunction with substance use. It has been suggested that since people seem to have the ability to assess their own CT, cognizance of a person's discrimination in CTs can be very operational in planning training programs and preventative health-associated methods for each one (Nasiri et al., 2019). This seems very appropriate to us, but specifying that the time of the evaluation is essential. The CT evaluation appears sensitive at the time of demand for treatment, while it may lose their sensitivity throughout the months that treatment is required (Antúnez et al., 2016; Capella et al., 2018).

The mismatch between sleep timing in workdays and free days can promote hazardous metabolic abnormalities as cardiovascular risks, greater insulin concentrations (De Hert et al., 2009; Wong et al., 2015; Casas & Roncero, 2016) and given the shortcoming in the treatment of DD patients, must of the studies agree with the emphasis that sleep irregularity in these patients should be given much more attention by the health and clinical organizations. Therefore, some researchers suggest preventive and therapeutic strategies in SUD (Timko et al., 2005; Chakravorty et al., 2018; Jones & McCance-Katz, 2019) and DDs (Deans & Soar et al., 2005; Guest & Holland, 2011; Daigre et al., 217) such as therapeutic alliance in SUD+SZ patients (Roncero et al., 2016). Needless to say, these suggestions in addition to pharmacological treatments in DDs (Lingford-Hughes et al., 2004; Malat & Kahn, 2011) should be incorporated in organizations to achieve promotion habits that benefit the CR (Haynes et al., 2006; Arnedt et al., 2007). In this regard, unhealthy eating habits during rest times are associated with the risk of obesity (Arble et al., 2009; Baron et al., 2011). Also, eating during usual sleep times may arise as a result of SJL (Wong et al., 2015). It has been postulated that MTs experience less stress because of using more healthy foods like fruits and vegetable intake (Haraszti et al., 2014b). Also, since substance use may affect appetite and eating habits, they both are among the risk factors in these patients. Hence, in addition to effective treatments, dietary guidance is highly recommended (Ross et al., 2012). Consequently, as already mentioned, physical activities including sport and dance and access to different types of non-

alcoholic drinks should be taken into account as preventive strategies for bad health habits (Popkin et al., 2010). These physical activities should be done outdoors under natural daylight (Adan, 2013). We recommend future studies to consider the effects and interaction of SJL, disrupted sleep and mealtime, especially in DD patients.

Although our results agree with some previous studies, to the best of our knowledge, a limited number of studies have been done on CR and DDs up to now**,** most of our research group. Future studies should consider this issue to achieve earlier prevention or even better treatments concerning CR misalignments in DD patients.

- **Sleep characteristic.**

As far as we know, this is the first study that considers the quality of sleep in DDs in comparison with SUD. As we expected, when the total score of PSQI is considered, SUD+MDD patients showed the worst scores followed by SUD+SZ and SUD groups even after controlling age and age of onset of SUD variables. Also, SUD+MDD group reported the worst scores in the sleep quality dimension, subjectively assessed, compared to SUD and SUD+SZ patients. However, these results are in line with previous studies on the depressed patients, where it is observed that those who reported worse sleep quality have more severe depression (Alvaro et al., 2014; Robillard et al., 2015; Selvi et al., 2018; Tonon et al., 2020). In this regard, a possible explanatory factor is that the SUD+MDD group reported the highest use of sleep medication (Antúnez et al., 2016), also maybe they suffer more emotional problems in the face of harder work and life with anxiety (Marquez-Arrico et al., 2019b) that can impact their sleep times in comparison with SUD and SUD+SZ groups. SPs and MDD are associated with low light exposure and reduced physical movement, so unstable social rhythms play a role in sleep and circadian interruptions in depressive disorders (Short et al., 2013a; Asarnow et al., 2014; Friborg et al., 2014; Matamura et al., 2014). Therefore, an irregular lifestyle and a decrease in daily light exposure contact influence the biological clock and mood of individuals and increase the possibility of developing an MDD (Jankowski, 2014; Antypa et al., 2017) therefore, the same can happen to SUD+MDD patients.

Regarding the sleep disturbance dimension, the SUD+SZ group showed the worst scores among the three groups. This result extends previous works which reported that negative symptoms and

cognitive deficits can cause sleep disturbances and even a high prevalence of insomnia in SZ patients (Cohrs, 2008; Waite et al., 2016). Besides, this result is in line with studies that observed higher sleep disturbance in SZ patients than BD patients and/or healthy groups (Afonso et al., 2014; Laskemoen et al., 2019). Our study extends this observation associated with patients with only SZ diagnosis to SUD+SZ patients. In contrary with previous work on SZ patients that higher irregularity sleep time was significantly associated with the worst PSQI scores, greater social rhythm irregularity and greater severity of positive symptoms (Cohrs, 2008; Xiang et al., 2009; Afonso et al., 2014; Chung et al., 2018; Korenic et al., 2020), the worst scores of PSQI in our study was reported in SUD+MDD group and we did not find any association with severity/presence of symptomatology of SZ (PANSS) in terms of sleep quality. It should be noted here that the previous data have not been obtained with DD patients, so the presence of SUD can influence the results of sleep characteristics associated only with the comorbid disorder (SZ and MDD). Cognitive-behavioral therapy for insomnia (CBT-I) targeting maladaptive coping strategies and intrusive thoughts (Izuhara et al., 2018) has been recognized as an effective method for improving sleep in SZ patients with insomnia and sleep irregularity (Edinger, 2001; Freeman et al., 2015). It seems that a multimodal approach also may be needed to evaluate this association (Harvey et al., 2016; Waite et al., 2016). Further research, however, is needed to delineate the causal relationship between sleep irregularity and negative outcomes or effectiveness of CBT-I in regularizing sleep-wake patterns of SZ patients, which can also be used for comorbid disorders.

Unlike the other studies that reported ET as a risk factor of various physical, psychiatric, and SPs in SZ patients (Fabbian et al., 2016; Margraf et al., 2016), we did not find any relationship between CT in clinical variables related to the SUD+SZ group. In agreement with previous works, we found that DDs, especially the SUD+SZ group, reported lower scores in dimensions of sleep latency (Lunsford-Avery et al., 2013; Afonso et al., 2014; Zanini et al., 2015); however, these studies only compared SZ and healthy control groups. Longer REM latency in previous work in SZ patients was explained by a reduction in activities and longer naps during the day (Zanini et al., 2015). Thus, our study suggests that since sleep abnormalities are as possible predictors of the shift to a severe mental disorder, further studies with a greater focus on CDs are needed to prevent further psychopathologies in individuals and society. Since most patients with SZ (Walther et al., 2009; Bromundt et al., 2011; Nyboe et al., 2016; Lee et al., 2018; Scheewe et al., 2019) or SUD+SZ (Benaiges et al., 2012; Río-Martínez et al., 2020) are not physically active it has been advocacy

for an active lifestyle as an important intervention to aid rehabilitative processes in them (Juel et al., 2017). In this sense, our data extend this observation to patients with SUD+SZ and also to SUD+MDD. Thus, it becomes necessary to consider in the treatment of DD some behavioral strategies including training in sleep hygiene with a focus on the regular wake and sleep times, preventing naps, enhancing activity during the day as physical exercise as a part of the therapeutic strategy (Pendlebury et al., 2007; Hjorth et al., 2014), exposure to enough light during the day (Vandewalle et al., 2006; Figueiro et al., 2014; Juel et al ., 2017), and sufficient darkness during the night (Barion & Zee, 2007; Adan, 2013).

In agreement with previous works, where poor sleep quality in MDD patients was reported as a major complaint (Monteleone & Maj, 2008; Dallaspezia & Benedetti, 2011; Shochat et al., 2014; Gobin et al., 2015; Müller et al., 2015; 2016a; Tochigi et al., 2016; Luca & Peris, 2020), we found this observation in the comorbid depressive group (SUD+MDD) in which can be exacerbated the loss of sleep quality due to the presence of SUD. Furthermore, we observed that the age of onset of SUD and severity of depression had a negative and positive relationship with the total score of PSQI in the SUD+MDD group, respectively (De Souza & Hidalgo, 2014; Müller et al., 2016). These results are inconsistent with previous work carried out in younger age and untreated depression individuals (Robillard et al., 2014). Finally, it should be noted that as expected the SUD group is the one with less consumption of medical drugs compared with DDs (Benaiges et al., 2012; Adan et al., 2017b; Marquez-Arrico, 2019b; Río-Martínez et al., 2020).

Regarding personality characteristics, have been observed scores in extreme poles of several traits related to maladaptive strategies in SUD (Giancola & Mezzich, 2003; Pence et al., 2008; Coriale et al., 2012; Marquez-Arrico et al., 2015; Adan et al., 2017b; Mason et al., 2020), and with a greater impact on SUD+MDD (Adan et al., 2017b; Marquez-Arrico 2019a, b) and SUD+SZ (Duijkers et al., 2016; Adan et al., 2017c; Sabater-Grande et al., 2020) patients. Besides, the DD groups scored higher in social withdrawal (i.e., avoiding any contact with those persons related to the stressful situation) and lower in engagement strategies such as problem-solving, cognitive restructuring, and social support than the SUD group (Marquez-Arrico et al., 2015, 2019b; Adan et al., 2017b, c; Río-Martínez et al., 2020). Also, in another works with nearly the same sample size but with (Marquez-Arrico et al., 2019a) and without follow-up sessions (Adan et al., 2017b), suggesting that DD patients use maladaptive coping strategies in related situations. Summarizing, DD patients

indicate more difficulties in asking for social support, and since social support is not a protective factor even in the follow-up sessions, a high rate of relapse to substance use is reported in these patients, especially in SUD+MDD ones (Marquez-Arrico et al., 2019a).

Although in some researches SUD+SZ patients showed worse scores in inhibitory tasks than SZs (Rodriguez-Jimenez et al., 2010; Duijkers et al., 2016), other studies (Jockers-Scherübl et al., 2007; Rodriguez-Jimenez et al., 2008) did not report any difference. The differences in results may have been influenced by the research samples, the differences in concomitant treatments and the severity of disorders. SUD+SZ patients with low Self-transcendence (Marquez-Arrico et al., 2019a; Río-Martínez et al., 2020), more self-criticism and social withdraw and less social support (Marquez-Arrico et al., 2015, 2019a) reported high substance use relapses that are in line with inefficient decision-making strategy in SUD+SZ patients with more suicide attempts than none attempters (Adan et al., 2017c).

Although discussion about the personality issues is beyond the scope of this study, some of their approaches may be used in dealing with DD patients regarding CR and sleep disorders, the evaluation of executive functions and therapies regarding cognitive remediation could be useful in the treatment. Overall, their results showed that some coping strategies are related to maladaptive clinical variables or the existence of SUD. Future studies should consider both coping strategies and social support in DD patients throughout the treatment process and psychotherapeutic plans. Moreover, it is recommended to avoid maladaptive strategies and replacing them with other adaptive ones (Adan et al., 2017b), depending on psychiatric diagnosis (Marquez-Arrico et al., 2019a; Río-Martínez et al., 2020). This target will not be achieved unless paying attention to the sleep-wake-cycle in mental disorder patients, especially the DD ones.

Although we did find not any interaction among CTs and the groups of patients, considering the total sample, both ETs and MTs reported worse scores than ITs in PSQI (quality of sleep). In line with this result, a previous study did not find relationship between sleep deprivation and CT (Zanini et al., 2015). The quality of sleep probably plays a more important role than the CT in the prediction of SUD (Zargar et al., 2012; Ghaseminejad et al., 2015). Although the association between CRs and mental problems is unclear yet (Miller et al., 2015; Togo et al., 2017) but taking CTs into consideration is an important key point in the mental disorders and requires more

attention in future studies. Nevertheless, according to previous works, connections among CR disruption, SPs and psychiatric disorders (McClung, 2007; Levandovski et al., 2011; Hickie et al., 2013; Alvaro et al., 2014; Kervran et al., 2015; Luca & Peris, 2020) arise from some postulations regarding the impact of the molecular clock on neurotransmitters systems (McClung, 2007) or come from differences possibilities in sleep-wake-cycles exposing to the light, which is a factor worsening the psychiatric disorders (Lester, 2015). In terms of quality of sleep, our results agree with some previous studies, but most of them only compared single disorders, and they were missing the precise impact of the mental disorder related to the quality of sleep in DD patients. The high prevalence of SPs in our study, regardless of the group, highlighted the importance of a precise assessment of sleep disturbances in future studies in SUD with/without comorbidity.

It is well evidenced that nocturnal light exposure is associated with insomnia and MDD (Adan, 2013; Obayashi et al., 2013, Keller et al., 2017). Also, in SZ patients' withdrawal, both social lifetimes and daylight can lead to further problems in CRs (Bromundt et al., 2011; Dallaspezia & Benedetti, 2011; Wulff et al., 2012). Up to 80% of patients with severe mental illness report sleep irregularities (Monti et al., 2013; Luca & Peris, 2020) that influence both their physical and mental health (Asarnow et al., 2014). Results recommend that timely regulation of sleep might act as a protective factor for behavioral problems in later development (Van der Heijden et al., 2013; Hühne et al., 2018; Repa, 2019). Since DD patients suffer from more psychiatric problems than a single disorder (Olivares et al., 2013; Antúnez et al., 2016; Adan et al., 2017a; Marquez-Arrico et al., 2019a), we see the possibility of a dramatic increase in exacerbating the severity of both SUD and comorbid disease. In sum, most published works on SPs in those with severe mental disorders such as SZ and MDD have been presented focuses on the psychopharmacological approach (Roth et al., 2006; NIDA, 2007; Conti et al., 2012; Mariani et al., 2014; Litten et al., 2016).

Recently, the CBT-I appropriately tailored for these patients (Klingaman et al., 2015; Boland et al., 2019) has been identified as a promising treatment for future research. Also, for SPs of severe mental disorders, moderate aerobic exercise has been recommended (Landolt & Gillin, 2001; Juel et al., 2017; Rubio-Arias et al., 2017). Exercise contributes to significant improvements in sleep parameters, depression symptoms, and immunological function (Passos et al., 2014), better stress management, less susceptibility to obesity (Shochat et al., 2014), and enhanced cognition and

metabolic functioning in the clinical population (Firth et al., 2015). In this direction, our work wants to convey the usefulness of considering chronobiological strategies both in the treatment of SUD and DDs.

To the best of our knowledge, this is the first study about sleep beliefs on DDs compared with SUDs. The psychometric properties obtained for the SBS suggest that components loading were low in some items, and dimensions items did not match to original Spanish scale (Adan et al., 2006). Therefore, by eliminating seven items of the original questionnaire (numbers: 1, 2, 10, 15, 16, 18, 20) we reached adequate factor analyses. The reduced scale, composed by 13 items, showed similar acceptable internal reliability (α=0.710) and dimensions including Sleep-incompatible behaviors with six items (α=0.594); Sleep-wake-cycle behaviors with four items (α=0.484) and Thoughts and attitudes to sleep with three items (α=0.546) to the original scale; but explained a higher percentage of variance with respect to the original scale. The corrected item-total correlation ranged from -.011 to .470. This seems a good option for the clinical populations of SUD patients with and without comorbidity in Iran.

Taking into account the deleted items we can make some considerations. Items 1 “Drinking alcohol in the evening” and 2 “Drinking coffee or other substances with caffeine after dinner” according to cultural differences due to the ban on alcohol consumption and different patterns of drinking in Iran (Habibisaravi et al. 2015) can be lead to the lowest scores among these 7 deleted items. In this regard, Iranian people drink more tea in the morning and evening and coffee is not considered as an ordinary drink among them. These results are in agreement with previous work (Adan et al., 2006) among Spanish and Italian students in respect to their CT and sleep beliefs. While Spanish ones reported coffee used as a high beverage consumption, Italian individuals especially men minimized the negative effect of alcohol and coffee or other substances with caffeine on their sleep. These are interesting cultural differences that we leave for future studies to adapt these questions according to their patterns of drinks of course with respect to the clinical or healthy subjects. The items 10 “Going to bed 2 h later than the habitual hour”, 16 “Going to bed 2 h earlier than the habitual hour” and 18 “Being worried about the impossibility of getting enough sleep” were also eliminated. Our study only composed by men, unlike women and consistent with Italian men participants (Adan et al., 2006) who reported a lower amount of think that going to bed and

waking up always at the same hour or being worried about the impossibility of getting enough sleep can impact on sleep. Except for cultural issues, since lower physical activity in psychiatric patients is more observable over time (Nyboe et al., 2016; Juel et al., 2017) can lead to less sensitivity to these questions in the clinical population. In line with our study, another work on Romanian depressed patients (Voinescu et al., 2010) reported that items 15 “Getting up when it is difficult to fall asleep” and 20 “Recovering lost sleep by sleeping for a long time” indicated low correlations with the total scores. Likewise, in our study, the patients minimized the negative effect of these questions that contributed a low correlation with respect to the total scores, so we decided also delete them.

According to the internal reliability for the SUD group in both original (α=0.820) and reduced SBS (α=0.803) questionnaires, this measurement scale runs better to assess and evaluate the beliefs of sleep compared to DD ones (SUD+SZ: α=0.701 and SUD+MDD: α=0.635). One of the advantages of the reduced SBS is less response time and for the Iranian population is more adapted and measures the desired indicators better than the original one. Summarizing, this scale despite being used in some countries with acceptable internal reliability, recommended and requires more multicultural studies to revise items according to the relevant cultural differences and taking to account sociodemographic and clinical aspects.

By reducing the items, we observed some different results in the reduced SBS compared to the original one. In the original SBS, Sleep-wake-cycle behaviors and Sleep-incompatible behaviors in the first analyses showed no differences between SUD+MDD and SUD but better than SUD+SZ groups, while the differences among the three groups in Sleep-wake-cycle behaviors eliminated in the second analyses by the age of onset of SUD. In other words, the second analysis showed that Sleep-wake-cycle behaviors are conditioned by age of onset of SUD among the three groups. In the reduced SBS, Thoughts and attitudes to sleep showed better scores in SUD+MDD and SUD groups compared with the SUD+SZ group. Totally, in all cases, the SUD+MDD and SUD groups showed better scores compared with the SUD+SZ group. Likewise, according to the total score of SBS, both SUD+MDD and SUD groups showed more belief tendencies toward sleep in the original and reduced SBS compared with the SUD+SZ group even after eliminating the confounding factors.

According to clinical variables related to original SBS, the severity of depression negatively and the age of onset of SUD positively had a relationship with Thoughts and attitudes to sleep in the SUD+MDD group. In the SUD+SZ group, the severity of the disorder had a negative relation with Sleep-incompatible behaviors. Instead for reduced SBS, number of substance use had a negative relation with both DD groups and the total sample in all dimensions of reduced SBS. Explaining, in the total sample, the number of substance use had a negative relation with Sleep-wake-cycle behaviors and Thoughts and attitudes to sleep. In the SUD+SZ group, number of substance use related negatively with Sleep-incompatible behaviors, severity of SZ negatively related with Thoughts and attitudes to sleep and in SUD+MDD group more Number of substance use related with lower scores in Thoughts and attitudes to sleep.

Summarizing, it seems that in the current study number of substance use and severity of disorders highlight the existence of a negative relation with the dimensions of sleep beliefs in DDs with respect to the clinical variables in both original and reduced scale. These results extended the recent finding (Chang et al., 2020) that dysfunctional beliefs about sleep were most observable in mood and psychotic spectrum disorder patients in comparison with anxiety disorders. Another study (Brooks et al., 2020b) found there is an association between dysfunctional sleep beliefs with worse sleep and higher relapse in SUD patients. Explaining this, the comorbidity may be associated with more behavioral symptoms and psychopathological problem (Brown et al., 2011; Antúnez et al., 2016; Adan et al., 2017a; Marquez-Arrico et al., 2019a, b) and could affect patient's perceptions and consequently leading to more dysfunctional beliefs of sleep. Although our DD patients showed low education degrees than SUD ones, in contrary with previous findings we did not observe that patients with low education levels report more sleep dysfunctional sleep beliefs (Friedman et al., 2007; Grandner et al., 2010; Chang et al., 2020), which can be due to different clinical groups, age range or even higher education levels that indicate a greater ability to deal with sleep concerns. We leave it for future studies to monitor the sociodemographic and clinical data associated with beliefs of sleep regarding clinical populations.

Regarding CTs, although no interaction between CTs and any group in the total SBS was observed in our study, we found that in both original and reduced SBS, both ITs and ETs got better Sleep-wake-cycle behaviors scores in the total sample compared to MTs. This is contrary to previous studies (Carney et al., 2007; Voinescu et al., 2010) that did not find any association between CTs

with sleep beliefs or its dimensions in the psychiatric patients. Also, contrary to (Adan et al., 2006) we did not find any association with MT and correct beliefs of sleep. One reason for the different results is this last research sample consisted only on healthy students and composed with female and male genders and since women tend to show better sleep hygiene practice than men (Man Park et al., 2002; Adan et al., 2006) or selecting only students was because of having fewer limitations on social synchronizers (Adan & Natale, 2002; Adan et al., 2012) it can influence the results. We selected among clinical men patients with and without comorbidity, with different constraints in social demands, a higher age range, more psychiatric medicinal drug users, having various religious, cultural and doctrinal values. All these can lead to different results compared to previous studies on CT related to the healthy or normal population (Morin et al., 2002; Adan et al., 2006; Adan et al., 2012; Antúnez, 2020).

Effective preventive intervention in SPs can be applied to identify incorrect sleep beliefs (Brown et al., 2002; Harvey et al., 2017; Brooks et al., 2020b) along with individual, medical and social variables. For this reason, longitudinal and intercultural studies with test-retest reliability of SBS and comparing with other standard measures to improve the diagnosis of SPs, especially in clinical samples, are recommended. Some results suggested a list of simple hygiene routine measures that have been confirmed to have a significant effect on improving nights' rest including reducing substance consumption, avoiding watching television, and or browsing social media late in the evening (Kooij & Bijlenga, 2013; Feliciano et al., 2019). In this regard, families going to bed on time also can establish earlier and more stable sleep wake-up times. Most research points out that sleep education may be effective in improving sleep beliefs (Morin et al., 2002; Dolan et al., 2010; Voinescu et al., 2010; Eidelman et al 2016; Harvey et al., 2017; Chow et al., 2018) found that CBT-I as a treatment to a reduction in scores of maladaptive sleep beliefs to achieve into sleep hygiene might be useful for particular therapeutic groups. However, a more in-depth research is needed to investigate the effects of CBT-I on sleep characteristics especially for targeting and changing dysfunctional sleep beliefs in SUD and DD.

5.3. Quality of life

This study is one of the few that has been done on the QOL of DD in comparison to SUD. The results extended previous findings that DDs have worse QOL in comparison with SUD (Benaiges et al, 2012; Aras et al., 2013; Lee et al., 2020). SUD patients were scored better in the overall QOL and all dimensions including Physical, Psychological, Social relationship, and Environmental health, even after controlling confounding factors like age and age of onset of SUD. Having better Physical health in SUD patients than DDs is in line with previous work (Benaiges et al., 2012). This study reported that SUD patients, because of less functional disability and more work activities, show more social communications than to DDs. DDs in our study reported worse Social relationships than the SUD group, regardless of whether they are SUD+SZ or SUD+MDD. This result is in agreement with the previous study in which DDs showed more difficulties in asking for support and less social network than SUDs and making friends (Marquez-Arrico et al., 2015; Adan et al., 2017b; Marquez-Arrico et al., 2019a, b).

In the current study, except for the Environmental health in the SUD group that was similar to the norm population, all three groups scored lower in all other dimensions of QOL compared to the normal population. In this regard, the SUD+MDD group in Physical and Psychological health, SUD+SZ group in Social relationships and Environmental health got the lowest scores. The SUD group showed the best scores in all domains compared to DDs. This result is in line with a previous work (Bizzarri et al., 2005), in which DD patients in the QOL gained lower scores than SUD ones, especially in Psychological and Physical health domains. In contrary to our results, another study (Wade et al., 2007) DD reported worse scores in the vitality but not in mental and Physical health domains compared to SUDs. Thus, patients with DD and SUD due to illness may have a more stressful life and subsequently worse QOL than normal people, which could associate negatively with treatment fulfillment and prevention of recurrence.

Although one study of heroin-dependent patients on methadone maintenance did not indicate significant differences in QOL of DD patients (Astals et al., 2008) almost all of the other studies reported worse QOL among these patients. In line with previous works that DD patients with higher quantity of substance use experience less QOL (Aras et al., 2013; Moreira et al., 2013) and are prone to more suicide attempts, morbidity and mortality (Degenhardt & Hall, 2001; Adan et

al., 2017b; Marquez-Arrico et al., 2019a), in our total sample of patients we found that number of substance use is negatively related to overall QOL. Findings including Physical health in SUD+SZ showed a negative relationship with SJL and suicide attempts. In accordance with this study, in previous researches, SUD+SZ patients showed more hospital contacts, more hospitalization, and more risk of dying during follow-up sessions than single disorder ones (Dickey et al., 2002; Schmidt et al., 2011; Frasch et al., 2013; Marquez-Arrico et al., 2019a). In this regard, researches showed that in treatment programs like social support (Lee et al., 2020) on QOL especially for the Physical health of the DD (Juel et al., 2017) or severe mental disorder patients (Hjorth et al., 2014; Giménez-Meseguer et al., 2015) is positively associated with the number of interventions attended.

We found that psychological health in SUD+MDD patients has a negative relationship with SJL, consistent with a previous study on healthy participants in which SJL was positively associated with depressive symptoms (Mathew et al., 2019). In a healthy population, one study also found an association among sleep time work end time, sleep onset time and psychological well-being (Carvalho et al., 2018). Therefore, it seems that SJL has an important effect on both healthy and clinical population, which may exacerbate MDD or SZ even in SUD patients. Thus, it is suggested conducting further studies by incorporating this parameter. Also, in the urban population, using devices such as smartphones and manipulating alarm clocks (McGlinchey & Harvey, 2015; Carissimi et al., 2016; Feliciano et al., 2019) has caused a deeper misalignment between social demands and biological clock. As a result, these factors strongly affect a person's life, especially physical and psychological functioning. Since adequate sleep is important for physiological performance and the timing of sleep is necessary for social demands (Vollmer et al., 2013; Shochat et al., 2014; Klingaman et al., 2015), more investigation is needed to consider the possible pathways that may influence and be influenced by SJL, social demands, and their interactions with the biological clock, especially in the clinical population (regarding more SPs) compared with healthy individuals.

Psychological health in SUD+SZ and SUD+MDD patients had a negative relationship with both severities of SZ and MDD. These results are in line with the previous study in which the functioning of SUD+SZ patients was worse than SZs (Solanki et al., 2008; Aras et al., 2013; Uludag & Gülec, 2016; Adan et al., 2017c) and SUD+MDD (Benaiges et al., 2012; Daigre et al., 2017). Physical health was associated with sleep latency in the SUD+MDD group, patients with

more Physical health reported less sleep latency. Besides, patients with higher Psychological health showed less sleep latency. Summarizing, the role of DDs has not been adequately analyzed in researches, especially in the QOL aspect and since poor sleep quality is linked to a low QOL in severe mental disorder patients (Klingaman et al., 2015; Subramaniam et al., 2018), any psychological (Wilson & Argyropoulos, 2012; Mulligan et al., 2016) and physical activity (Juel et al., 2017) improvement in people with a severe mental disorder is contingent on improving sleep parameters that can be applied for DD (Torrens et al., 2015; Juel et al., 2017) patients.

Our results denoted that SUD+SZ patients with more Social relationships reported fewer suicide attempts and lower severity of SZ. A study on Indian SZ patients (Solanki et al., 2008) also observed a negative relationship between PANSS and the Social relationship. In accord with this result, it has been reported that in DD patients the suicide attempts and more substance consumption may be associated potentially with lower QOL (Benaiges et al., 2012; Chahua et al., 2015). Similar results have been reported in insomniac SZ patients with a lower social relationship (Hofstetter et al., 2005; Hou et al., 2017; Subramaniam et al., 2018). It is possible that SPs lead to a lack of energy, daytime dysfunctions, and finally, more stress (Ritsner et al., 2004) impairing the QOL of SZ and SUD+SZ patients.

Our data are consistent with previous works, where patients with more QOL reported a higher quality of sleep (Xiang et al., 2009; Klingaman et al., 2015; Subramaniam et al., 2018) or patients with less sleep disturbance showed more QOL (Bromundt et al., 2011; Pritchet et al., 2012). We extended these works and highlight that patients with more Physical, Psychological, and Environmental health shown higher sleep quality and less sleep latency, sleep medication, and daytime dysfunction. Thanks to previous studies and given to our results in which highlight the impact of circadian functioning, sleep characteristics, and QOL in severe psychiatric disorders, especially DD, further research is needed in this area. Overall, according to the results of previous research on the healthy and patient individuals, it seems that sleep problems and related factors lead to exacerbating difficulties in both populations and may underlie as precipitating factors in the development of severe mental illness or DDs.

Some reasons for not receiving the necessary care the DD patients include lack and high cost of treatment, stigmatization, treating only mental illness or SUD separately, having a medical care

system that does not put enough emphasis on the recognition or treatment of comorbidities, and having a medical education system that allocates very little training/teaching time to this clinical population and a good management requires a good perception of the efficacy, interactions and side effects of pharmacological and psychological treatments of these patients (McGovern et al., 2014; Szerman et al., 2014; Torrens et al., 2015; Daigre et al., 2017; Juel et al., 2017). Consequently, handling the prevention programs or treatment processes by exerting and inspired the research results is much more cost-effective and can dramatically double the chance of success of the treatment protocol (Ialongo et al., 2001; Teesson & Proudfoot, 2003; Harouni et al., 2017; Torrens et al., 2017; Subodh et al., 2018; Lee et al., 2020). Many centers devoted to the treatment of drug dependencies have employed chronobiological behavioral strategies in their programs (Adan, 2013; Capella et al., 2018). Because of enhanced QOL of the patients and creating a protective factor against relapse after the treatment sessions, patients are recommended following healthy time habits (Falcón & McClung, 2009; Adan, 2010c; Capella et al., 2017). These include regular time patterns of meals, daily physical and social activity and sleep-wakes synchronized to the light-dark cycle (Grandin et al., 2006; Kosobud et al., 2007). As a result, individuals lead to having better physical, intellectual, and emotional performance (Asarnow et al., 2014), as well as more mental health (Owens, 2014). Our data emphasize that this line of complementary therapeutic approach seems essential in the treatment of SUD and even more so in DD, whether the comorbid disorder is SZ or MDD.

6. STRENGHS, LIMITATIONS AND FUTURE RESEARCH

In this study, we provided new data over previous research on the topic of SUD and DD. The evidences of clinical factors associated with SUD and DD Iranian patients under treatment has been provided. We sought new data in exploring circadian functioning, sleep characteristics and QOL for the first time in SUD patients with and without comorbid severe mental disorders. Our study had other strong points as an accurate diagnosis of each group even according to family history and an exhaustive evaluation of circadian functioning. Additionally, an appropriate number of patients in each group was included, especially in DDs compared to most of the previous research. Also, we achieved to reduce SBS with an optimal factor analyses similar acceptable internal reliability to the original SBS, with explaining a higher percentage of variance and with less response time. This was necessary due to cultural aspects that influenced the responses to the eliminated items.

Despite its advantages, this study had some limitations as well. Our sample is comprised of non-randomized groups without a control group, and we used a cross-sectional design. Besides, the loss of patients during the research was another limitation that may influence the results. In this regard, although our cross-sectional study design permitted us to ascertain the weight of each psychiatric condition in the three groups, it did not allow us to see the casual relations between SUD and comorbid psychiatric disorders. The suicide attempt was collected by the self-report and was retrospectively but without recording the method of attempting and seriousness, although we compared this information with medical records we do not exclude that such data might be biased. It is the first study made in this line in Iran so our results can be not generalized to other mental disorders. Therefore, suggests that future studies investigate more aspects of severe mental disorders comorbid to SUD or SUD without comorbidity according to their circadian functions, sleep characteristics and QOL to achieve the optimum levels in treatment programs. Despite the use of confounding factors such as age and age of onset of SUD as covariates in the analysis, we did not explore their possible role in the obtained results.

Only the male gender investigated, so it is suggested considering also female gender in future works. In addition while this study covered different ages of patients, the large age range may have

contributed to the type-II error on the other hand it can limit the generalization of the results. In European countries, women account for less than 20% of all patients treated in drug addiction centers and this is even more evident in Iranian centers. The same happens with the SUD+SZ diagnosis, a minority in women. To study a comfortable number of women, we should approximately triple the patients considered, although it is undoubtedly necessary to address their possible differential characteristics both within and between groups. However, this exceeded the temporally limited sample collection possibilities of the present work. Due to a lack of access to abstinence time and the severity of substance use among patients, we suggest that future studies take in to account these variables for a more detailed and in-depth among their clinical variables.

Given that past research highlighted that the type and even number of substance use vary depending on the location and geography of each region, participants in this study are no exception to this rule and included a limited geographical area. For future studies, we suggest considering this issue as well. Besides, this study relied on the retrospective self-report methods, which is susceptible to recall bias and may not completely reflect their true characteristics; future research should be conducted to prevent and minimize this bias. Furthermore, as far as possible it would be necessary to introduce objective measures of circadian functioning that will allow a qualitative leap in the quality of the information collected. We were not able to examine the possible independent effects of the different types of substances used or the prescription of psychotropic drugs in the patients and may have an impact on the outcomes. Since the percentages and combinations of substance use were not similar among groups, further studies should be conducted with larger samples to elucidate this aspect that is essential and can mediate the results.

Our design has been able to address the influence of the comorbid disorder with respect to the presence of only SUD in sociodemographic and clinical characteristics, circadian functioning and QOL. However, in the future, the inclusion of groups with only the comorbid disorder (SZ and MDD) will be required to fully assess its specific gravity in DD associated with the diagnosis without SUD. Despite the weaknesses mentioned, the current study is an important first step to consider circadian characteristics and QOL in SUD, SUD+MDD, and SUD+SZ patients under treatment. Longitudinal designs are needed for a more detailed study of possible associations between sleep characteristics and circadian functions. Ideally, patients should be included at the time they access the resource requesting treatment for SUD and measurements should be scheduled

at various times during treatment, including objective records of circadian rhythmicity and sleep. A follow-up of two years from inclusion seems the most indicated, considering the duration of treatment proposed by the WHO. This exceeds the possibilities of a doctoral thesis, it already requires a long project in time and with sufficient research and clinical staff, but without a doubt, it is the way forward for progress in this field of research.

7. CONCLUSION

Co-occurrence of substance use and severe mental disorders is highly prevalent, this condition is known as Dual Diagnosis (DD) and is associated with a major or worse prognosis for both addictive and psychiatric disorders. Several studies indicated that the most prevalent mental disorders among patients with SUD are Schizophrenia (SZ) and Major Depressive Disorder (MDD). We decided to explore as the first study, the circadian functioning including sleep characteristics, and the QOL of SUD patients with MDD and SZ comorbidities in Iran.

Regarding sociodemographic and clinical data, SUD+SZ patients were much younger and single, SUD+MDD patients had more illiterate individuals while SUD ones were the only group with more frequency of university graduated. In SUD+SZ patients the age of onset of SUD was younger. More concomitance of organic pathology, a higher amount of psychiatric disorders history, also more suicide attempts was more noticeable in the SUD+MDD group. On the other hand, SUD patients reported more law or legal problems compared to DD groups. SUDs reported the highest rate of opium and crystal use, while the highest number of substance use was observed in the SUD+SZ. The present study is in line with some previous Iranian works on the type of substance use, although it adds further information on the characterization of DD patients, very little data is available despite the importance for more depth interventions in the future-focused on secondary psychiatric symptoms to achieve better adherence and therapeutic results.

We did not find any significant difference among groups in SJL but SUDs showed a tendency to go to bed later than SUD+MDDs and SUD+SZs both during the workdays and the free days (weekend). SUDs were more likely to be IT and lower to population norms. SUD+MDD patients were more prone to be MT, and similar to the normal population, the SUD+SZ patients were more likely to be ET with lower scores than the normal population. An association between CTs and polydrug use showed that the highest rate of polydrug users were reported to be ET in interaction with the diagnoses.

Despite little research with DDs in the field of sleep quality, most of them report that those with worse sleep quality have more pathological problems. In line with these findings, DD patients showed worse sleep quality among the three groups in our study. In this regard, the SUD+MDD

group reported the worst scores in the sleep quality scale (PSQI), subjectively assessed among the groups, even after controlling age and age of onset of SUD variables, with a higher number of problem in sleep quality dimension and more medicine sleep intake. The SUD+SZ group showed the worst scores among the three groups in the sleep disturbance dimension. The age of onset of SUD and the severity of MDD showed negative and positive relationships, respectively, with the total PSQI scores in the SUD+MDD groups. Our results agree with some previous studies that psychiatric patients suffer irregular sleep but most of them only compared single disorders, and they were missing the precise impact of the mental disorder related to the quality of sleep in DD patients. Since we did find not any interaction among CTs and the groups with respect to the sleep quality reinforce this idea that the quality of sleep probably plays a more important role than the CT in the SUD and DD. In other words, regardless of the patient's CT, when a mental disorder has developed, it and its severity seem to be the best indicators of sleep disturbances. Moreover, the high prevalence of SPs in our study, regardless of the group, highlighted the importance of a precise assessment of sleep disturbances in future studies in SUD with/without comorbidity.

As we know, this is the first work on sleep beliefs on DDs comparing with SUD. Although the internal reliability for dimensions of original SBS was low in all cases, by eliminating seven items with respect to the low correlation with the total scores and low interaction with cultural aspects, we reached optimal factor analyses. Reduced SBS has less response time and for the Iranian population more adapted and measures the desired indicators better than the original one. In the total score of original and reduced SBS, the SUD+MDD and SUD groups obtained better scores compared to SUD+SZ group. According to clinical variables related to original SBS, the severity of depression negatively and the age of onset of SUD positively related to Thoughts and attitudes to sleep. The severity of the SZ disorder had a negative relation with Sleep-incompatible behaviors. In the reduced SBS, the number of substance use negatively related to the dimensions in both DD groups and the total sample. Consequently, this study highlights that better scores in dimensions of sleep beliefs are related to a lower amount of the number of substance use and severity of disorders.

To date few researches have been done on the QOL of DDs, but almost describe the DD patients more affected than SUD ones and they face to more problematic lifestyles, even after controlling confounding factors. Except for the Environmental health that in the SUD group it was the same

as the norm, and all the three groups obtained lower scores than the Iranian normal population in other dimensions. We found that number of substance use is negatively related to overall QOL. As well as, previous suicide attempt was linked negatively to Physical and Social relationship dimensions in SUD+SZ group. SJL and severity of MDD had negative relationship with Physical health and those with more Physical health had less sleep latency in SUD+MDD group.

This research shows strong points as an accurate diagnosis of each group even according to family history and an exhaustive evaluation of circadian functioning of an appropriate number of patients in each group. We achieved to reduce SBS with an optimal factor analyses similar acceptable internal reliability to the original SBS, due to the need for cultural adjustments. Moreover, there are limitations from our study that have to be taken into account for future works. Our sample was comprised of non-randomized groups composed only by men, a control group was not included, and as a cross-sectional study it was not possible to explore casual relations. We suggest that future studies take these concerns into account to develop new designs that overcome them.

Overall, our design has been able to address the influence of the comorbid disorder with respect to the presence of only SUD, highlights the importance of attention to the circadian functioning, sleep characteristic and quality of life of patients with DD concerning their sociodemographic and clinical variables. Hence, future studies should consider our results with respect to mentioned limitations for knowledge promotion in this scope and related outcomes to design better and more effective treatment processes. Furthermore, handling the prevention programs by exerting and inspired the research results is much more cost-effective and can dramatically double the chance of success of the treatment protocols.

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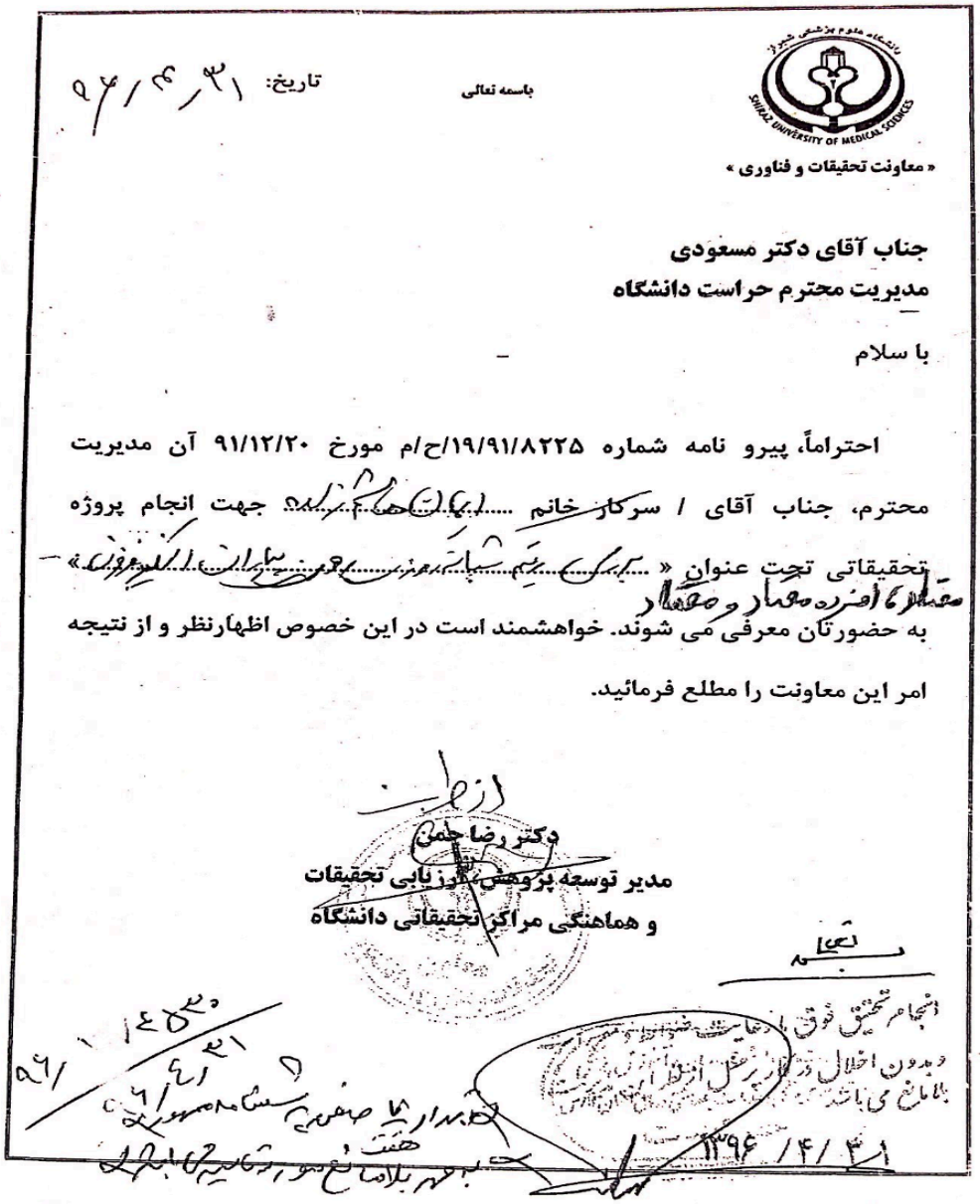
9. ANNEXES

9.1. Confirmation of ethics committee of Shiraz University of medical sciences (Annex 1)



باسمه تعالی

تاریخ: ۹۶/۴/۳۱

« معاونت تحقیقات و فناوری »

جناب آقای دکتر مسعودی
مدیریت محترم حراست دانشگاه

با سلام

احتراماً، پیرو نامه شماره ۱۹/۹۱/۸۲۲۵/ح/م مورخ ۹۱/۱۲/۲۰ آن مدیریت محترم، جناب آقای / سرکار خانم ..... جهت انجام پروژه تحقیقاتی تحت عنوان « ..... » به حضورتان معرفی می شوند. خواهشمند است در این خصوص اظهارنظر و از نتیجه امر این معاونت را مطلع فرمائید.

دکتر رضا جمالی
مدیر توسعه پژوهش، ارزیابی تحقیقات
و هماهنگی مراکز تحقیقاتی دانشگاه

9.2. Informed consent (Annex 2)

فرم شرکت در پروژه تحقیقاتی

با تشکر از همکاری شما مراجع محترم در پروژه تحقیقاتی با مضمون بررسی کارکرد ریتم شبانه روزی، خواب و همچنین سبک زندگی در بیماران مرکز تخصصی اعصاب و اعتیاد به اطلاع میرساند هدف از این تحقیق تعمیق دانش در مورد درک بهتر ریتم های خواب و بیداری، اختلالات خواب و سبک زندگی بیماران میباشد. از این نتایج میتوان برای بهبود هر دو روش پیشگیری و درمان بیماران استفاده کرد. این جلسات شامل ۲ روز کاری شده که به شما پرسشنامه هایی مبنی بر نوع بیماری و سبک زندگی و خواب شما ارائه خواهد شد روز اول اطلاعات کلی شخصی و روز دوم پرسشنامه های ارزیابی ریتم شبانه روزی و سبک زندگی داده خواهد شد.

لازم به ذکر است که اطلاعات دریافتی از شما به صورت محرمانه است و فقط توسط مرکز تخصصی و درمانگران مربوطه مورد ارزیابی قرار خواهد گرفت.

اینجانب آقای .....اعلام میکنم که حضور من با رضایت و آگاهی کامل بوده و ضمن موافقت خود جهت شرکت در پژوهش مذکور، مختار هستم هر گاه بخواهم از مشارکت خود انصراف دهم.

با تشکر از همکاری شما

امضا بیمار امضا درمانگر

9.3. Social demographic and clinical data (Annex 3)

سن:

وضعيت تاهل :

1. مجرد .2 متاهل .3 مطلقه .4 بيوه

وضعيت كاري:

1. شاغل .2بيكار. .3 بازنشسته

ميزان تحصيلات :

1. ابتدايي .2راهنمايي .3 دبيرستان .4دانشگاهي

ميزان در آمد:

1. متوسط به بالا .2متوسط
2. متوسط پايين .4 ضعيف

سابقه بيماري جسمي :

بله. خير. شرح دهيد.

سابقه بيماري اعصاب:

بله. خير. شرح دهيد.

سابقه خودكشي :

بله. خير.

وجود بيماري اعصاب در خانواده درجه اول : بله. خير.

شرح دهيد.

وجود سابقه اعتياد در خانواده درجه اول: بله. خير.

شرح دهيد.

مشكل خانوادگي: بله خير.

مشكل قانوني: بله خير.

مشكل شغلي : بله خير

سابقه مصرف كدام مواد مخدر زير را داريد؟ (توجه كنيد كه با توجه به سابقه مصرفي، هر چند گزينه را ميتوانيد پر كنيد)

1. قليون. .2سيگار. .3 شيشه. .4هروئين. .5 غيره (شرح دهيد)

9.4. SBS questionnaire in Persian (Annex 4)

این یک نظر سنجی از اثرات رفتارهای مرتبط با خواب است.
ما از اینکه نظر شما را در این مورد که آیا این رفتارها ممکن است بر کیفیت یا کمیت خواب اثر بگذارد، بدانیم ، بسیار علاقمندیم . برای لیست رفتارهای زیر، لطفا مشخص نمایید که آیا شما باور دارید که این رفتارها بر خواب تاثیر مثبت ، منفی و یا بدون اثر دارند. هنگام پاسخ به سوالات لطفا به یاد داشته باشید ، بدون ارجاع به خواب شخصی خود، تاثیر این رفتارها را روی خواب عموم مردم در نظر گرفته و همه سوالات را علامت بزنید. با تشکر از همکاری شما .

	اثر مثبت بر خواب دارد	اثر منفی بر خواب دارد	بی اثر است
۱.مصرف الکل در عصر			
۲- مصرف کافه یا دیگر نوشیدنیهای کافیین دار بعد از شام			
۳-انجام تمرینات سخت فیزیکی قبل از خواب			
۴- چرت زدن طولانی مدت درطی روز			
۵- خوابیدن و بیدار شدن در یک زمان مشخص و همیشگی			
۶- دل مشغولی درباره گرفتاریهای روز بعد			
۷- استفاده از داروهای خواب آور بطور منظم			
۸- مصرف سیگار قبل از خواب			
۹- خالی کردن ذهن از مشغله و سپس آرامش قبل زمان خواب			
۱۰- رفتن به تخت خواب، ۲ ساعت بعد از زمان خواب همیشگی			

	اثر مثبت بر خواب دارد	اثر منفی بر خواب دارد	بی اثر است
۱۱- خوابیدن با شکم خالی			
۱۲- استفاده از تخت برای خواندن، زنگ زدن و کار با تلفن، مطالعه و یا دیگر فعالیتهای غیر مرتبط با خواب			
۱۳- تلاش در به خواب رفتن بدون احساس خواب آلودگی			
۱۴- مطالعه یا کار شدید تا دیر وقت			
۱۵- برخواستن از خواب در مواقعی که به خواب رفتن مشکل است			
۱۶- رفتن به تخت خواب، ۲ ساعت قبل از ساعت همیشگی			
۱۷- رفتن به تخت خواب درست بعد از صرف غذا			
۱۸- نگرانی درباره نداشتن خواب مناسب			
۱۹- خوابیدن در یک اتاق ساکت و تاریک			
۲۰- بازیابی خواب از دست رفته قبلی ، با خواب جایگزین طولانی مدت			