Unveiling sleep mysteries: Sleep-wake cycle as a biological parameter of the circadian typology (Chronotype)

Revelando mistérios do sono: Ciclo sono-vigília como parâmetro biológico da tipologia circadiana (cronotipo)

M. da Mota Gomes[1]

"Hark, hark! the lark at heaven's gate sings,
And Phoebus `gins arise,
His steeds to water at those springs
On chaliced flowers that lies;
And winking Mary-buds begin
To ope their golden eyes:
With every thing that pretty is,
My lady sweet, arise:
Arise, arise."
William Shakespeare's Cymbeline: Act 2, Scene 3

ABSTRACT

The sleep-wake cycle that is circadian rhythm may have different patterns according to sex, environment and genetics determinants. This chronological cycle type, chronotype, may be populational expressed by the extremes, early or later going to bed and waking up, in a continuum. The first, the Morning-type individuals (the lark) and the later, the Evening types (the owl). Between the two extremes, there is the majority of these chronotypes – the intermediate ones. These patterns may be classified according to the questionnaires such as Horne and Ostberg Morningness/Eveningness Questionnaire (MEQ) and the Munich Chrono Type Questionnaire (MCTQ). The rural population tends to be Morning-type, as well as children and younger women, more than men. The Morning person tends to be more healthy than the Evening ones who are more prone to diseases, as depression and metabolic syndrome. This basic knowledge may be helpful to patient's counseling and management: to avoid mismatch of circadian physiology and social duties / sleep. This circadian desynchrony can increase the risk of diseases, consequently there is a need to chrono-medicine into current treatment strategies.

Keywords: Circadian rhythm, Chronotype, Morningness–eveningness, Sleep-wake cycle

RESUMO

O ciclo sono-vigília, que é um ritmo circadiano, pode ter padrões diferentes de acordo com os determinantes sexuais, ambientais e genéticos. Esse tipo de ciclo cronológico, cronótipo, pode ser expresso em termos populacionais pelos extremos, indo cedo ou mais tarde para a cama ou saindo dela, em um continuum. O primeiro, os indivíduos do tipo Manhã (a cotovia) e o posterior, os tipos da Tarde (a coruja). Entre os dois extremos, há a maioria desses cronotipos - os intermediários. Esses padrões podem ser classificados de acordo com questionários como o Horne e Ostberg Morningness/Eveningness Questionnaire (MEQ) e o Munich Chrono Type Questionnaire (MCTQ). A população rural tende a ser do tipo matutino, assim como crianças e mulheres mais jovens, mais que os homens.A pessoa da manhã tende a ser mais saudável do que as da noite, mais propensa a doenças, como depressão e síndrome metabólica. Esse conhecimento básico pode ser útil para o aconselhamento e tratamento dos pacientes: para evitar incompatibilidade entre a fisiologia circadiana e os deveres sociais / sono. Essa dessincronia circadiana pode aumentar o risco de doenças, consequentemente, é necessário a cronomedicina nas atuais estratégias de tratamento.

Palavras-chave: ritmo circadiano, cronotipo, ciclo sono-vigília

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INTRODUCTION

The sleep timing disposition, chronotype or circadian typology, is an individual variable highly relevant for both health and well-being. Human chronotype can be assessed by the timing of an individual's sleep-wake cycle, and it is linked to the sleep need that comprise about one-third of adult human life. Consequently, it can be recognized by different phase relationships between the expression of circadian rhythms and external synchronizers in humans. Besides, the adequate chronotype, the sleep duration and quality are all recognized important for health and well--being. Particularly, an individual's chronotype reflects how the circadian system incorporates itself into the 24-hour day physiological rhythms, what includes the cognition and behavior, and also the preferred wide-ranging of timing of sleep and wakefulness[20].

It is remarkable, that the biological rhythms are endogenous and cannot be manipulated by the subject, but a person with social schedule times that conflict with his/her own biological rhythm may have reductions of health, quality of life and performance. Paine et al., [17] accomplish that morningness/eveningness possibilities are largely autonomous of ethnicity, gender, and socioeconomic position, which indicates that it is a constant characteristic that may be better elucidated by endogenous factors. Indeed, interindividual differences in the circadian processes are molded by genotype, ontogeny, environment and gender[13].

An individual's chronotype, with morningness/eveningness bias, is prone to the definition of periods of best performances and well-being. This basis can be used to optimize the quality of life and to reduce the impact of any associated disturbance.

In this paper, they are presented the temporal sleep patterns, its epidemiological profile and biological basis, all prone to be used for patient health counseling.

CIRCADIAN SYSTEM AND INDIVIDUAL PROFILE

The circadian system regulates rhythmicity in the body and the suprachiasmatic nuclei (SCN) constitutes the main human pacemaker known as the biological clock, but other parts of this system also cover the pineal gland, retina, and retinohypothalamic tract. In particular, a circadian rhythm is any biological process that presents an endogenous precise rhythm oscillation of about 24 hours that are determined by a circadian clock, and the sleep-wake cycle is a light-related circadian rhythm (**Figure** 1).

There is an interaction between circadian rhythms and the environment, as occurs with the daily light-dark cycle, being the light the main zeitgeber (time giver) of the biological clock. This external information is transmitted to the suprachiasmatic nucleus (SCN) through the retinohypothalamic tract[1] (**Figure 2**).

It is now known that there are molecular clocks in most tissues and cell types, and that the circadian system is a network of oscillators dispersed all over the brain and periphery[13]. In addition, several cues have been identified, including food, locomotor activity, and social tips. Besides, the SCN works closely with the pineal gland which produces melatonin, which is the darkness signal in the organism, and it is considered the best marker of the endogenous circadian pacemaker[1].

The SCN synchronizes circadian rhythms by autonomic, behavioral, humoral, and temperature mechanisms, and consequently human behavior, physiology and metabolism are subject to daily rhythms. It is remarkable, that melatonin release begins again in the late evening and it promotes sleepiness, likewise, body temperature begins to drop. In addition, cortisol levels peak in the morning, alertness increases throughout the morning, and motor coordination and reaction time are best during the afternoon.

It was found that Sporting peak performances occur in the late afternoon and early evening, approximately at the peak of central body temperature[9]. In addition, the circadian phase markers (temperature, melatonin, and drowsiness objective time) were 2-3 hours later for evening-types than for morning-types. However, according to previous studies, the differences in subjective sleepiness rhythms were much greater (5-9 hours) [3,14].

The timing and duration of sleep are controlled by the circadian system, and a portion of the sleep chronotypes variation in the population is controlled by genetics but also environmental factors as shown by the single-gene mutations that confer extreme early or late chronotypes. There are various circadian rhythmicity outputs such as biochemical, physiological and, behavioral, but the most discernible is the sleep–wake cycle. In all the cases there are differences among chronotypes although depending on the parameter they are of a higher or lesser magnitude[1].

The molecular basis of the circadian clock is a transcriptional-translational autoregulatory feedback loop of the products of a panel of clock genes[13]. This genetic basis is now understood and the molecular circadian clock is

formed by a negative feedback loop involving the Period (PER1, PER2, and PER3) and Cryptochrome (CRY1 and CRY2) genes, besides others[11]. Probably, the most considered human gene variant regarding its role in diurnal preference is a PER3 polymorphism, e. g., such as hPer3, with 4 or 5 repeats - 54 bp in exon, in Brazilian population regarding delayed sleep phase syndrome[2]. Besides, several twin and family studies suggest that genetic factors appoint a considerable proportion, up to 50%, of the population variability in circadian timing[1,11].

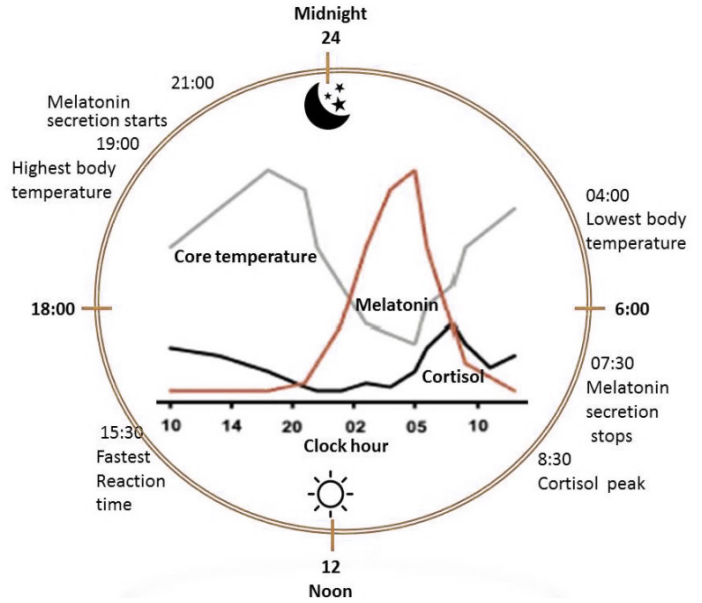


Figure 1. The circadian rhythms in humans. Rhythms that vary according to the time of day, such as the sleep-wake cycle and the changes in body temperature, melatonin and cortisol. Line chart based on Amirian[3].

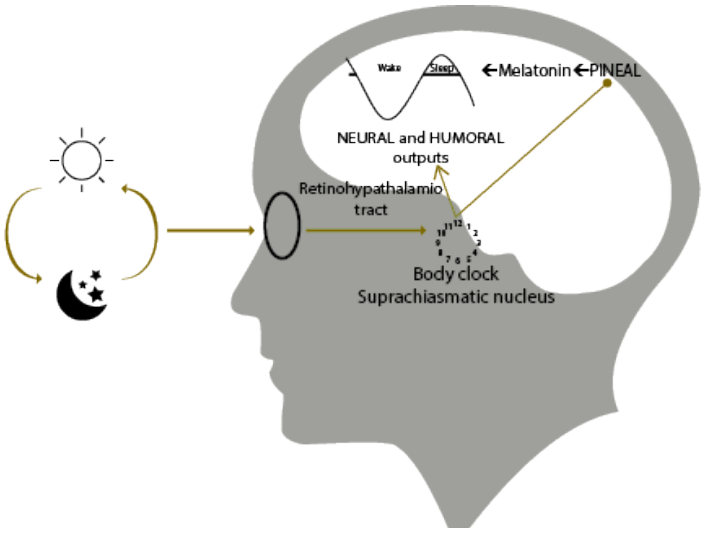


Figure 2. Circadian Timing System. The light-dark cycle is the primary external synchronizer, or zeitgeber of the central circadian pacemaker (suprachiasmatic nucleus - SCN, via the retino-hypothalamic tract). Environmental clues include besides the light-dark stimulus, meal schedule, temperature and physical activity, as well as endogenous signals. The SCN modulate the organism's rhythms, through the neural pathway (Autonomic Nervous System-SNA) and the humoral pathway to control e. g. melatonin production by the Pineal gland. Melatonin is absent or untraceable low during the daytime.

This extremely important subject led to the 2017 Nobel Prize in Physiology or Medicine that was jointly awarded to Jeffrey Hall, Michael Rosbash, and Michael Young. They worked in the discovery of the mechanism that supports the circadian rhythm by means of studies on fruit flies[5].

Chronotype measurement

The assessment of chronotype ranges from biological measures such as dim-light melatonin onset (DLMO) to questionnaires, but currently, the most reliable measure of circadian phase in the human master clock is the DLMO[12]. However, chronotype is usually assessed through self-assessment questionnaires, such as The Horne and Ostberg-Morningness/Eveningness Questionnaire (MEQ) and Munich Chronotype Questionnaire (MCTQ), among others. These are the questionnaires used in the surveys presented at the table.

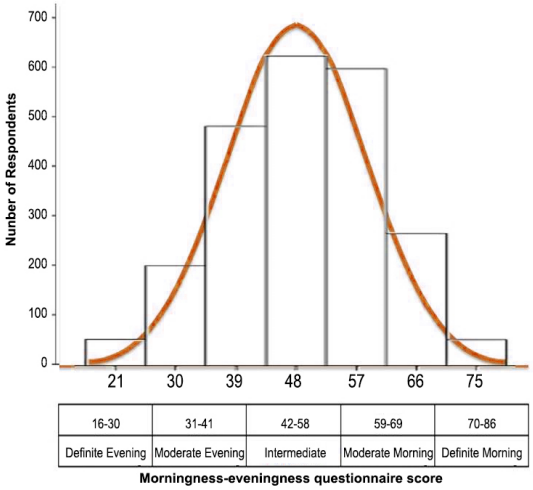
Regarding the first questionnaire, the MEQ is the most widely used and validated instrument[10]. The MEQ assess morningness and eveningness and the questions are enclosed in a special way, where the respondent is asked to show when, e. g., he/she would wish to wake up or start sleep, rather than when he/she actually does, and the scale is composed of both Likert type and time-scale questions. The first presents four options with the lowest values indicating definite eveningness. Regarding the second, the time-scale items are divided into periods of 15 min spanning a time frame of 7 h. The sum gives a score ranging from 16 to 86. Scores of 41 and below indicate "evening types", between 42-58 point,"intermediate types", 59 and above, "morning types" (**Figure 3**). In conclusion, the MEQ inquires about the favorite daily timing for an array of activities that conceives an arbitrary score.

There is also a 5-item short form (reduced morningness-eveningness questionnaire (-rMEQ) that is particularly valuable in the situation of a large-scale survey[1]. The total scores of the 5-item rMEQ range from 4 to 26, with cutoff scores for determining chronotype groups: eveningness: < 12; neither: 12–17; morning: > 17.

By contrast, the Munich Chronotype Questionnaire (MCTQ) collects additional detailed information on sleep-wake behavior under natural conditions[22]. A particularly valued feature of the MCTQ is the distinct management of work and free days. It focuses primarily on sleep timing self-rated scale to assess individual phase of entrainment

on work and work-free days. This is an instrument to gather primary sleep times, such as bed- and rise-times, plus the clock time of becoming fully awake as well as sleep latency and inertia, in addition to other time points and rate themselves as one of the chronotypes. The MCTQ uses the mid-point between sleep on- and offset on free days (mid-sleep on free days, MSF) to evaluate chronotype. It is composed of 17 items in 4 domains (work schedule, workday sleep schedule, free day sleep schedule, self-assessment of chronotype[26]. In short, the MCTQ asks and utilizes the actual sleep-wake times on work and work-free days to determine chronotype by the mid-point of sleep on days off. Although, it is not categorical but permits to define population-specific thresholds and thus delimits chronotypes.

The actigraphy (or accelerometry) is frequently used to monitor human sleep/wake cycles. Besides, it is also applied in epidemiological studies about sleep chronotypes such as that of Matuzaki et al. [15], in São Paulo-Brazil. The authors used the MEQ and Actigraph for at least three consecutive days in 359 adult subjects for characterization of the temporal patterns of sleep and wakefulness. The results demonstrated that the actigraph objectively assessed



the sleep-wake cycle and was capable of differentiating between morning and evening type individuals.

Figure 3. Distribution of Horne and OstbergMorningness/Eveningness Questionnaire (MEQ) scores. It shows a bell-shaped curve population distribution, with extreme late types fall asleep until extreme early types waking up based on the histogram by Zavada et al. [26]. Below, the proposed scores cut-off points of the MEQ[10].

CHRONOTYPES POPULATIONAL DISTRIBUTION

The distribution of human chronotypes forms a near-Gaussian population distribution, with the extreme - morning-type and evening-type, at its ends[2] (**Figure** 4). This classification comprises three circadian types: the morning, the intermediate and the evening. Morning-type individuals show an orientation for going to bed and waking up early, and accomplish the peak of their mental and physical performance in the early part of the day. On the contrary, evening-types reach their peak towards the end of the day.

Two important factors that affect the chronotype are age and sex , but human chronotype is partly influenced by genetic factors[2]. Indeed, the chronotype distribution is largely derived from genetic polymorphisms in clock genes, development (age), mainly in adolescents, and the environment[21]. Consequently, zeitgeber strength such as more light in the morning than in the evening may explain differences between individuals, and on the contrary, living indoors and nighttime illumination may explain eveningness[21].

The table 1 presents the principal characteristics of different population chronotype according to epidemiological surveys in the use of MEG and MCTQ measurements. The morning-type is more frequent until age 10, and from age 50 on. Moreover, most of the studies hold that the tendency toward morningness increases with age. The population studies also find higher morning-type in girls and women, but the sex differences disappear following menopause in women[1]. Roenneberg et al. [20] also reported women to be morning-type than men for most of the adulthood; however, this difference disappeared after the age of 50. In general, the population studies also find a higher evening-type prevalence in males, but that fades over the ageing.

Children were most frequently morning-type with adolescents being increasingly later and presenting a maximum of it at around the age of 20. After 20, chronotype was earlier again with increasing age. Duarte et al.[7] in a sample of Brazilians, demonstrated a different interaction between age and sex because women were also morning-type chronotypes than men up to the age of 30, but this was reversed in age groups older than 45. According to Roenneberg et al.[20] this difference against European studies might be population-specific, e.g., geographical location and the associated variations in sunrise, sunset and day length that are important factors for entrainment of the circadian clock, and consequently for chronotype. Besides, they may also be due to the use of different instruments to assess chronotype because Duarte et al.[7] applied the MEQ, but Roenneberg et al. [20] and Tonetti et al. [24] both used the MCTQ.

Regarding other Brazilian studies, some are linked to the Baependi Heart Study on a rural family-based cohort sample in a highly admixed rural population with a tradi-

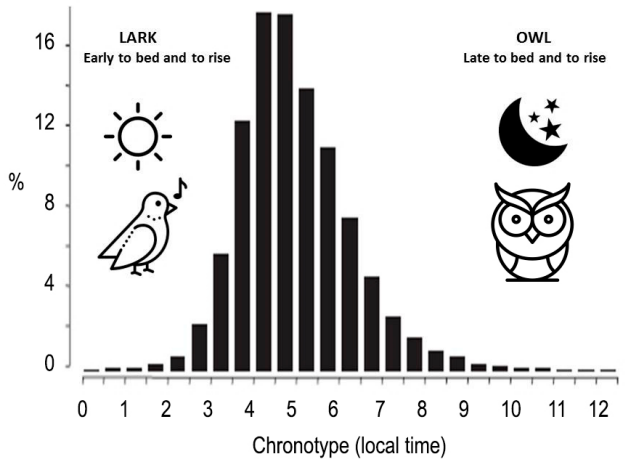
tional lifestyle. Von Schantz et al.[25] studied the distribution and heritability of diurnal preference (chronotype) of it. The authors recognize that in spite of universal access to electricity, the population was strongly shifted towards morningness, particularly in the rural zone. In the same population, Egan et al.[8] found, using the MEQ, that Amerindian ancestry (but not African or European) genetic ancestry is significantly associated with diurnal preference within an admixed Brazilian population, after adjustment for age, sex, education, and residential zone. Furthermore, Beijamini et al. [4] studied the timing and quality of sleep of this sample. It is known that increasing age was associated with earlier sleep time and shorter sleep duration, but, in particular, women slept longer and later, and they claim poorer sleep quality than men. In this study, the authors concluded that they show indirect evidence in the sustenance of the hypothesis that sleep timing was earlier prior to full urbanization.

The study by Matuzaki et al.[15,] carried out in São Paulo-Brazil with the use of the MEQ and Actigraph in 359 adult subjects shown that the morning type subjects were more frequent and older maybe because of the light exposure would be an environmental factor that is associated

Table 1. Epidemiological surveys aimed at collecting temporal sleep patterns based on conventional sleep chronotype questionnaires

Study	Population (n)	Main measurement (chronotype)	Main findings regarding chronotype
Zavada et al. (2005)[26], in Netherlands	5,055 responders (MCTQ), of which 2,481 (and MEQ).	MCTQ supplemented with MEQ	The progressive advance of sleep times with increasing age. Workday sleep onset became progressively earlier from the age group I (25 yrs) to age group IV (39 yrs).
Paine et al. (2006)[17] in New Zealand	2,526, from 30 to 49 yrs, randomly selected from the electoral rolls (55.7% response rate).	MEQ	49.8% morning type, 5.6% , evening-type.New cutoffs for middle-aged working adults, 24.7% morning type, 26.4%, evening type. Night workers are more likely to be definitely evening type. Evening types were 2.5 times more likely to disclose that their general health was only poor or fair in comparison to morning types. After controlling for ethnicity, gender, and socioeconomic deprivation, subjects 30- 34 yrs more likely to be evening type than those ages 45 to 49 yrs. Morningness/eveningness preference is mainly autonomous of these factors, it is a stable characteristic that may be better clarified by endogenous factors.
Roenneberg et al. [20] (2007)	55,000 (pool)	MCTQ	Sleep and wake times show a near-Gaussian distribution. The timing and duration were of sleep generally independent. Both examined independently for work and free days, sleep duration strongly rest on chronotype. Chronotype is both age- and sex-dependent. Children, generally earlier, progressively becoming later (delaying), reaching a maximum later around the age of 20, and then becoming earlier again with increasing age. Women reach maximum lateness around 19.5 yrs of age, men continue until around the age of 21 and are, on average, later chronotypes for most of their adulthood
Tonetti et al. (2008)[24], in Italy	8,972 participants (5,367 females and 3,605 males) from 10 to 87 yrs of age	MEQ	Change to eveningness from the age of 13 yrs. Females got their highest in eveningness earlier (about 17 yrs of age) than males (about 21 yrs of age). Females presented a more significant advanced sleep phase than males only during the yrs when sex hormones are typically active. Females reported a longer ideal sleep duration than males, except in over 55 yrs.
Duarte et al. (2014)[7], Brazil	14,650 participants from ≈20 to >60 yrs	MEQ	On average, women were more morning-oriented than men until the age of 30 and there were no significant differences between men and women from 30 to 45 yrs of age, but women older than 45 yrs were more evening-oriented than men. Men have a larger amplitude of chronotype changes throughout their aging process.
Carvalho et al. (2014)[6], in Brazil	5942, 18–65 yrs, females (67.1%)	MCTQ	The rural population presented a more predominantly early sleep pattern, less social jetlag and higher light-exposure, higher prevalence of psychiatric disorders and a lower prevalence of metabolic diseases than urban.
Randler et al. (2016)[18], in German	14,987 visitors to an exhibition. 5–70 yrs. Females (54%)	rMEQ	Younger children are more morning adapt and turn rapidly into evening oriented all along the adolescence, while towards back in direction to morningness occurs from the age of 20 yrs. Then between the ages 25 to 30 morningness-eveningness continue rather stable. Significant gender differences existed in 16–50 yrs. In summer months more evening oriented. Men more evening oriented.
Sládek et al. (2020)[23], in Czech Republic	8759 subjects aged 10+	MCTQ	Chronotype showed noteworthy differences between east-to-westward, north-to-southward, and settlement size-dependent gradients and was associated with age, sex, partnership, and time spent outside. Women are normally slightly earlier chronotypes than men when they are young, but the difference fades with their older age. Subjects younger than 40 yrs, childcare was highly linked to earlier chronotype, while dog care was related to later chronotype.

MEQ-Horne and Ostberg Morningness/Eveningness Questionnaire (MEQ); rMEQ= reduced Morningness-Eveningness- Questionnaire; MCTQ=Munich Chronotype Questionnaire.



with the phenotypic expression of morningness. Sládek et al.[23], in Czech Republic, also demonstrated the differences in settlement size-dependent gradients.

Figure 4. Early, Intermediate or Late circadian phenotype groups. From Morning (Early, lark), through intermediate until evening (late, owl) chronotypes. The scale from lark to owl is continuous and histogram is by Roenneberg et al.[20] based on the mid-sleep time on free days corrected for the sleep-debt accumulated during the workweek and further corrected for age- and sex-dependent changes (MSFsasc).

CHRONOTYPE BIOLOGICAL AND COGNITIVE-BEHAVIORAL DIFFERENCES

As already seen, the circadian rhythms are also expressed by human behavior, physiology and metabolism. In special, the typical day favors a morning orientated individual, consequently this type displays psychological well-being, as daily behavioral rhythms are aligned to his social work schedule[13]. On the contrary, evening orientated individuals are likely to experience more sleep debt and circadian misalignment due to social/work schedules.

Evening-type individuals go to sleep and wake up 2–3 h later than the morning-type, although, there are no differences in the total amount of sleep if the individuals are free to choose when to sleep[1]. In contrast, the sleep times of morning-type individuals are more stable, without significant differences between working and nonworking days[1].

With respect to personality traits, several works have found important associations with them and the chronotypes: Larks (psychological wellbeing) and owl (negative health and behavioral outcomes).

Some people are morning-type and rise early and are more active in the morning, and, extraversion, agreeableness, and conscientiousness were related to morningness Others are evening-type and sleep late, being more active in the evenings and late nights and also tend to sleep more on weekends. Apparently having built up a sleep debt during the week more than morning-type do due to early work and school schedules. Besides, evening-type has shown and openness to experience and neuroticism according to Randler et al.[19].

When these tendencies are very strong and interfere with the person's daily life they may have a circadian rhythm sleep disorder, Advanced sleep phase syndrome, lark, or Delayed sleep phase syndrome, owl.

As already presented, there are several outputs according to circadian rhythmicity, biochemical, physiological or behavioral), and the sleep-wake cycle is one important one. In all these outputs there are differences among chronotypes, of higher or lesser magnitude[1].

IN CLINICAL PRACTICE

The epidemiological studies present indication establishing a link between the circadian clock and human health, besides mutant mice capably present the principle that dysregulation of the circadian system drive to several disorders[21]. Consequently, living out of phase with one's body clock will also bring circadian dysrhythmia, and has also been revealed to end in diseases[16].

Regarding human physiology, it has cyclical nature over a 24-h period, consequently, the effect of circadian rhythms can no longer be ignored in clinical sceneries. This knowledge was unfolded in the field of chronobiology, and its incorporation into daily practice to improve patient outcomes[16]. Chronic circadian rhythm disruption has been related to varied disorders, from metabolic disorders, obesity, diabetes, cardiovascular disease and cancer[16]. Consequently, interactions between the circadian clock and disease may whichever be direct or indirect via behavior and/or sleep. Besides, social schedules put forth their impact on physiology mostly via behavior[21]. The resultant misalignment in the evening-type may have various negative health and behavioral outcomes such as increased Circadian rhythms disorders, body mass index; major depressive disorder; type 2 diabetes; metabolic syndrome[13]. Consequently, "chronopathology" arrives when this harmony is lost. In conclusion, being evening-type is a risk factor in developing a delayed-phase sleep syndrome, especially during adolescence or

early adulthood as well as insomnia in adulthood. In contrast, being morning-type is a risk factor to present an advanced-phase sleep syndrome in the last decades of life[1].

In this way, circadian misalignment and mistimed sleep may be associated with risk of disorders, besides, health losses can arise from both sleep deprivation and circadian misalignment, common both in shift workers[21].

It is recognized that the circadian misalignment and discrepancy between social time (when an individual's sleep and wake time is dictated by social or work obligations) and internal biological time[13]. Consequently, novel behavioral interventions to reduce social jetlag may be simple yet important in both preventing and treating common side effects of circadian misalignment[13].

In regard to the above concerns, chronobiological strategies are recommended that includes regular time patterns, light therapy, and melatonin administration. They can be effective in several situations and have been proven to be secure even in special populations[1]. Consequently, Chrono-medicine is one of the most important upcoming themes in the field of circadian biology, and treatments counteracting circadian dysregulation are already being applied, as prescribing strong and regular zeitgebers[21].

In particular, it is emerging the "chronotherapeutics" that is the timing of an intervention or administration of a drug at the time of day where it is probable to have the ideal outcome[16].

Closing this section, it is remembered that being a morning-type may be a defensive influence for numerous deleterious outcomes, whereas being evening-type may be a bad risk factor. Thus, chronotype should allow both health prevention and also therapeutic approaches.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

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