Insomnia and sleep deprivation in patients with epilepsy: issues about the pathophysiological interaction between them

Insônia e privação de sono em pacientes com epilepsia: questões sobre a interação fisiopatológica entre eles

Marleide da Mota Gomes - https://orcid.org/0000-0001-8889-2573

ABSTRACT

There is a known relationship between seizures and sleep deprivation that increases epileptiform abnormalities and slow waves expressed in the EEG, but chronic insomnia, greater in patients with epilepsy (PWEs) than in healthy control, supposedly has a different mechanism linked to a hyperarousability state with increased rapid EEG activity and associated “restless REM”. Therefore, there is a complex interaction at various levels between insomnia and epilepsy that may play a role in seizure presentation. The recognized interconnection between mood and anxiety disorders and insomnia should also advise special care in the management of psychiatric comorbidities in PWEs.
This article raises questions related to the interaction between the brain basis of insomnia and epilepsy and the triggers of seizures, particularly sleep deprivation

Keywords: Epilepsy, sleep, insomnia, hyperarousability, sleep deprivation

RESUMO

Há uma relação conhecida entre crises epilépticas e privação de sono que aumenta as anormalidades epileptiformes e as ondas lentas expressas no EEG, mas a insônia crônica, maior em pacientes com epilepsia (PCE) do que no controle saudável, supostamente tem um mecanismo diferente ligado a um estado de hiperexcitabilidade com aumento da atividade rápida do EEG e associado “REM inquieto”. Consequentemente, existe uma complexa interação em vários níveis entre a insônia e a epilepsia que pode desempenhar um papel na apresentação das crises. A reconhecida interligação entre transtornos de humor e ansiedade com a insônia também deve aconselhar um cuidado especial no manejo das comorbidades psiquiátricas do PCE.
Este artigo levanta questões relacionadas à interação entre a base cerebral da insônia e da epilepsia e os desencadeadores de crises epilépticas, principalmente a privação do sono.

Palavras-chave: Epilepsia, sono, insônia, hiperexcitabilidade, privação de sono

Institute of Neurology Deolindo Couto, School of Medicine, Federal University of Rio de Janeiro

Corresponding author: Marleide da Mota Gomes, e-mail - mmotagomes@acd.ufrj.br
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INTRODUCTION

Patients with epilepsy (PWEs) present with a variety of major comorbid sleep disorders such as obstructive sleep apnea and insomnia which must be screened for and treated regularly. Equally, sleep and epilepsy are mutually related in a bidirectional complex relationship what was the subject of a previous review by the same author[13]. Some people have their first and only seizures after long sleep deprivation, and some types of epilepsy are especially prone to sleep problems and sleep-related seizures.

Sleep is considered restorative, essential for promoting general health and well-being, and is also involved in neuronal circuits and signalling that have a beneficial role in memory consolidation and synaptic plasticity[14]. On the contrary, insomniac has persistent and increased somatic, cognitive and brain cortical stimulation [4 6 23 25 31 33 36].

The chronic insomnia disorder according to ICSD-3 (International Classification of Sleep Disorders, 3rd Edition, American Academy of Sleep Medicine 2014) and the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, American Psychiatric Association 2013) includes a report of sleep onset, sleep maintenance or early waking problems, despite adequate opportunity and circumstances for sleep, besides daytime impairment of functioning or well-being, for 3 months, and at least at three times a week[33].

Another issue concerns partial sleep deprivation, less studied than experimental total sleep deprivation, which is related to a chronic restriction that is often experienced due to medical and sleep comorbidities, work demands, social and domestic commitments, and lifestyle[1]. As for the frequency of insomnia symptoms in the general population, it affects about a third of the general population[33]. Besides, it has also long been known that psychiatric disorders may be an important risk factor for insomnia, but not necessarily a cause of it, but it is only recently that the prevalence of insomnia in PWEs has begun to be investigated.

Consequently, the general population is often affectedby symptoms of insomnia, and presumably PWEs with a brain disorder with a long-lasting predisposition to generate epileptic seizures would also be, as several studies indicate as shown in the next section[20].

This intricate relationship between insomnia and epilepsy leads to this brief and updated review that addresses a trigger of epileptic seizures such as sleep deprivation, in addition to studying the relationship between chronic insomnia and epilepsy, especially regarding neurobiological issues.

INSOMNIA IN PATIENTS WITH EPILEPSY

Both symptoms of insomnia and insomnia disorder in adult PWEs have substantially higher prevalence compared to controls, based on a limited number of studies with variable inclusion criteria and methodology[20]. Some are presented in Table 1, highlighting the prevalence of insomnia according to Insomnia Severity Index scores (ISI), and summarizing their results on the relationship between epilepsy severity and psychiatric disorders. The ISI is a brief assessment of insomnia, consisting of seven questions about problems with sleep over the past two weeks. The first three items concern the severity of sleep onset, sleep maintenance and problems waking up in the morning, and the subsequent items assess the degree of satisfaction or dissatisfaction with the current sleep problem, interference with daily functioning, perception of the impairment attributed to the sleep problem, and amount of concern due to the current sleep problem. The total scores range from 0 to 28[21 34].

Insomnia is increasingly recognized as a cause of reduced sleep quality in PWEs, and insomnia symptoms and insomnia disorder were generally more frequent in them than in non-epileptic subjects. In several studies, insomnia was associated with greater impairment in quality of life and a greater degree of depressive symptoms, and it was also inconsistently related to the female sex, poor seizure control, and polytherapy with antiepileptic drugs (AEDs). Thus, insomnia symptoms are highly prevalent in adult PWEs and are frequently associated with depression, anxiety, and the results reported so far have been inconsistent with the impact of insomnia on seizures, as some studies conclude that there is, but others have not found this association[20].

Regarding characteristics related to epilepsy with insomnia, Macedo *et al*.[20] found that a higher Insomnia Severity Index score corresponded to decreased duration of epilepsy in two studies, although the insomnia disorder was more frequent in patients with nocturnal seizures, post-traumatic epilepsy, and on lamotrigine therapy.

The studies in the literature review by Macedo *et al*.,[20] that found a relationship between insomnia and refractory seizures did not show a relationship between insomnia and polytherapy, although these patients are more likely to be on at least two AEDs, drugs that can influence sleep architecture and they can also lead to sleep disturbances that are likely to enhance with increasing dose or number of these medications. Lamotrigine and felbamate are clinically recognized for producing insomnia, and a study showed that lamotrigine is independently related to the insomnia disorder in military veterans with epilepsy, by Lopez *et al*., apud Macedo *et al*.[20].

Regarding excessive daytime sleepiness, it was not related to insomnia disorders or symptoms, and the exclusion of individuals with it may explain insomnia higher prevalence found in some studies. This sleepiness, in addition to being comorbid with a sleep disorder, may also be due to the deleterious effect of nocturnal seizures on sleep architecture or sedation caused by AEDs[20].

Table 1. Some recent studies on epilepsy and insomnia, highlight the high prevalence of insomnia symptoms in PWEs and their relationship with the frequency of seizures and psychiatric comorbidities.

Insomnia Severity Index	Yang et al. Cleveland Clinic, USA (n=90)		Macedo INDC-UFRJ, Brazil (n=41 vs 83)		Gomes MM INDC-UFRJ, Brazil n=70 (interim analysis), not published			Planas-Ballvé et al., Badalona, Spain	
0–7 = No clinically significant insomnia	34.5%		51,2% vs 69,9%		55.9%			49,6%	
8–14 = Subthreshold insomnia	65.5%		48,8% vs 30,1% p = 0,032		44,1%		26.5%	50.4%	
15–21 = Clinical insomnia (moderate severity)		28.9%		22% vs 12%, p = 0,150		17,6%	13.2%		17.8%
22–28 = Clinical insomnia (severe)							4.4%		
Relationship insomnia vs seizures	No*		ISI ≥ 8, ≥ 3 seizures / previous year, p 0,019. ISI ≥ 15, ≥ 3 seizures / previous year, p 0,166		ISI ≥ 15, ≥ 3 seizures / previous year p 0,724			Yes. ISI ≥ 15, "poor seizure control" (≥ 1 seizure/month)	
Relationship between insomnia and psychiatric comorbidities	Yes		Yes		Yes			"factors independently associated with poor seizure control", OR: depression, 3.74; insomnia, 1.9.	

ISI: Insomnia Severity Index, INDC-UFRJ=Institute of Neurology, Federal University of Rio de Janeiro. *another study by the same Group found that poorer seizure control was associated with insomnia symptoms (r=0.31, p<0.001)[30].

SLEEP PHYSIOLOGY, SLEEP DEPRIVATION, INSOMNIA AND EPILEPSY, AND RELATED RISK FACTORS

Sleep physiology

Sleep chronology is regulated by complex homeostatic (Process S) and circadian(Process C) processes at various functional, spatial and temporal levels that include different brain circuits, cell types and molecules, as outlined in figure 1.

Among the biological rhythms, the circadian, circa 24 h, and the ultradian, less than 24, are closely linked with the sleep-wake and sleep cycles, of special interest of this paper. The ultradian rhythm of sleep consists of 4-5 cycles of about 90 min each formed by phases (rapid eye movement -REM, and non-REM -NREM- and NREM sleep that is subdivided into three - N1, N2, N3) which proceed in successive order during the night. The slow waves have an impact on homeostatic sleep regulation, and spindles and ripples provide plastic changes to the susceptible córtex[14]. These same NREM sleep constituents appear to be also linked to IEDs that may influence sleep plastic functions, as well[14]. Consequently, NREM sleep facilitates epileptic phenomena, which in turn, conflict with sleep functions.

Besides, it has long been known that REM sleep is characterized by the alternation of two microstates, one with rapid eye movements (phasic REM) and the other without rapid eye movements (tonic REM)[11]. Phasic REM may reflect increased desynchronization, but IEDs, ripples and fast ripples were more common in tonic REM sleep[11].

Also, the NREM has the cyclic alternating pattern (CAP), EEG microstructure recurring activity, that can be used to identify sleep instability[28]. The CAP is constituted by cerebral activation (phase A) followed by deactivation (phase B), and the first includes events as K-complex sequences, delta bursts, alpha waves, vertex sharp transients and arousals[28]. Sharma *et al*.[28] presented the conclusion that CAP rate (CAP time/Sleep time) increases in depression and also in: Movement behavior disorder, 0.49; Insomnia, 0.51; Narcolepsy, 0.53; Nocturnal frontal lobe epilepsy, 0.63; Periodic leg movement disorder, 0.68; Sleep-disordered breathing, 0.78.

The core of the sleep-wake program is constructed by genetic factors, but it is regulated by the systems of maintenance of wakefulness and the sleep promotion, and the circadian Process C seems to drive both wake- and sleep-promoting behavior, aiding the maintenance of wakefulness during the day, while at night, sleep[10]. The sleep-wake circadian rhythm is controlled by the suprachiasmatic hypothalamic nucleus, the 'master clock' in mammals, which is mainly regulated by light exposure, with melatonin expression that increases a few hours before bedtime, promoting sleep, with light exposure reducing the secretion of melatonin and interrupts sleep. However, the data obtained indicate that the circadian clock is less susceptible to light when sleep pressure is high[7].

The homeostatic process (Process S) refers to the accumulation of sleep pressure in response to prolonged wakefulness with the consequent compensatory somnolence that occurs after sleep induction, and several agents have been implicated in driving it, mainly adenosine[10].

Transitions between sleep and wakefulness are affected by two competing sets of brain circuits: one that promotes wakefulness and the other, sleep. For the former, several neurochemical systems promote excitation and rapid cortical activity typical of wakefulness, with monoaminergic neurons in the rostral brainstem and caudal hypothalamus directly innervating the cortex, as well as many subcortical regions, including the hypothalamus and thalamus. Signs of promoting wakefulness also arise from the parabrachial nucleus and cholinergic regions[27].

For the promotion of NREM sleep, GABAergic neuron pathways inhibit wake-promoting neurons in the caudal hypothalamus and brainstem, besides the basal forebrain also inclose neurons active during sleep that can support sleep through projections within the basal forebrain and direct projections to the córtex[27].

The transitions between sleep and waking states depend on the relative strengths of the two opposing sets of circuits and the result has been described as similar to a "flip-flop switch"[25]. As proposed, it would exist hybrid states of consciousness that may happen in several sleep disorders, and the concept of insomnia as a hybrid state was first advocated by Cano and Saper, apud Perlis *et al*.[23].

Sleep influences the onset of seizures, particularly in certain epileptic syndromes, but conversely, epilepsy can also interrupt sleep, either directly through seizures and interictal epileptiform discharges (IEDs), or indirectly through drug-related effects. Thus, the interactions between sleep and epilepsy indicate that NREM sleep and idiopathic generalized epilepsy share the same thalamocortical networks[14].

Also common is that most neurotransmitters and neuromodulators, such as adenosine, melatonin, prostaglandin D2, serotonin and histamine, in addition to regulating sleep-wake behavior, are likewise considered to have antiepileptic effects. In turn, AEDs can influence sleep too[32]. Jain and Glauser[16] identified in their systematic review that most AEDs interfere with sleep architecture: gabapentin, tiagabine, pregabalin, clobazam and carbamazepine, reducing latency and/or improving sleep efficiency; phenobarbital, valproic acid and high doses of levetiracetam aggravate excessive daytime sleepiness, whereas topiramate and zonisamide do not. Regarding lamotrigine, the authors retrieved only five class III studies, in two, with patients with refractory epilepsy. This drug increased REM sleep and reduced slow-wave sleep, but only one study evaluated subjective nighttime sleep, showing that no patient reported insomnia .

Furthermore, IEDs tend to be expressed during NREM sleep, where synchronization occurs more, whereas EEG desynchronization inhibits the spread of seizures during REM sleep as in wakefulness, and the lack of muscle tone blocks the seizures clinical expression [32 34]. Likewise, it is well established that both focal and generalized IEDs increase during NREM sleep, whereas REM sleep suppresses generalized, but in focal discharges, there is a good topographical relationship with localized anomalies. This accuracy of REM-IEDs localization is higher for temporal than extra-temporal epilepsy[35].

As already mentioned, NREM and REM sleep have opposite effects on seizures and IEDs in PWEs, and the thalamocortical oscillations that operate during the first can favour the occurrence of seizures, the activation and dissemination of IEDs. During REM sleep, IEDs are strongly reduced and this inhibitory effect is mainly exerted by its phasic component and this effect may be mediated by cholinergic neurotransmission, which markedly suppresses the occurrence and propagation of both interictal spikes and pathological high-frequency oscillations [11].

In counterpart, insomnia disorder is characterized by heightened environmental alertness that may exhibit a shift toward tonic REM sleep states[29], but the effect of tonic REM sleep is not significantly different from that of NREM sleep that favors seizures[29]. In conclusion, insomnia has a drive to tonic REM component that is less antiepileptic than the phasic one[11 29]. Consequently, to improve potential therapeutic approaches, the underlying mechanism of the protective influence of phasic REM sleep on epileptic activity needs to be better understood, as well as the relationship between epilepsy and insomnia, as the latter has an increased tonic REM component.

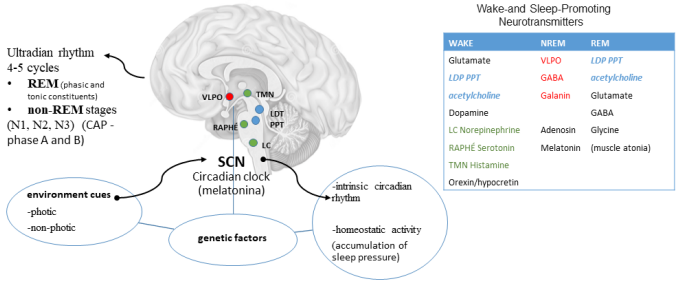

Figure 1. The neurophysiology and neurochemistry of sleep-wake control. Critical brain structures and functions[7 10 29 27 28]. TMN=tuberomammilary nucleus, VLPO= ventrolateral preoptic nucleus, PPT/LDT=pedunculopontine and laterodorsal tegmental nucleus, SCN=suprachiasmatic nucleus.

Sleep deprivation and insomnia. Commonly reported triggers of a seizure

Before going to the next section about insomnia and epilepsy, it must be stressed that sleep deprivation/sleep loss is not synonymous with insomnia by many experts in Sleep Science, in spite both insomnia and sleep deprivation involve failing to get enough sleep.

The first refers to a shorter duration than the average basal need of 7 to 8 hours per night due to an externally imposed restriction of the opportunity to sleep that usually is a modest reduction of sleep hours over long periods. Its daytime impairment includes excessive daytime sleepiness and reduced concentration, slower thinking, and mood changes.

Regarding insomnia, it implies having difficulty falling asleep, maintaining sleep, or short sleep duration, despite adequate space for a full night's sleep, besides, the insomniacs show increased subjective sleepiness but decreased objective one, regarding their over-aroused, but they feel subjectively tired[33].

Mild sleep deprivation activates the cerebral cortex and brainstem to generate the physiological drive to sleep, but chronic sleep restriction is different. The application of the multiple sleep latency test presents progressive shortening caused by a greater propensity to sleep, but, in insomnia, this same test tends to increase the drive to stay awake according to the patient's propensity for hyperarousability. However, Roehrs *et al*., apud Fietze *et al*.[9], despite finding higher sleep latency in insomniacs compared to healthy controls, found that the difference was small and the variability among insomniacs was high. Consequently, there may be possible subtyping of insomnia

according to the tendency to fall asleep during the day. Furthermore, the cognitive response of individuals differs considerably about sleep restriction, probably also due to their underlying genetic profile[1].

Epilepsy has underlying factors, triggers and patterns that differ between patients, with consequent unpredictability of seizures and patient apprehension, but their recognition is also important for nonpharmacological therapy. Consequently, a causal study is very complex as other factors may influence it, in this case, between the trigger factor and subsequent seizure.

Bartolini *et al*. [2] say that external seizure precipitants are mostly patient-reported and are highly subjective, and altogether, PWEs report at least one seizure precipitant, being emotional stress, sleep deprivation, and tiredness, irrespective of the underlying syndrome, besides, emotional stress, all reported by over 80% of them. Besides, anxiety and depression are especially common in PWEs whose seizures are worsened by emotional stress.

Alcohol intake, as chronic abuse or binge drinking, is another common trigger.Illicit drug abuse may also negatively affect seizure control, and seizure exacerbation may also result from exposure to very specific provocative stimuli such as the case of the so-called 'reflex seizures' that are consistently and objectively induced by identifiable and specific triggers. Another seizure precipitant is fever, mainly for specific epilepsy syndromes[2].

Ge *et al*. [12] studied the relative frequency of different seizure triggers in a survey of the US population of 598 PWEs enrolled in the EpiWatch study over an initial 10-month period: 177 participants reported stress (37%), lack of sleep (18%), menstruation (12%), overexertion (11%), diet (9%), lack of medication (7%) and fever/infection (6%). In this survey, seizure triggers did not vary by types of seizures, but the stress was more commonly reported as a trigger among participants working full-time (35.0%), compared to those working part-time (20.8%), unemployed participants (27.3%), or disabled participants (28.6%).

Concerning a study by Samsonse et al. 26, on sleep loss as a trigger for seizures, out of 144/179 consecutive hospital admissions for epileptic seizures were studied: sleep pattern before the seizure; the use of alcohol, caffeine and drugs; the results of the application of the Hospital Anxiety and Depression (HADS) Scale and a visual analogue scale for stress perception. Sleep time during the 24 h before the attack was shorter compared to follow-up; caffeine consumption and use of relevant non-antiepileptic medications were not different; HADS and admission stress scores were not related to the difference in sleep time; interaction with alcohol intake was high, but the difference in sleep time remained highly significant also for no and low consumption. The authors conclude that although precipitants of seizures are frequent and combined, sleep loss appears to be an independent trigger of seizures. In addition, sleep-deprived patients were younger than those without, and generalized seizures tended to be more common than focal seizures, mainly generalized genetic epilepsy syndromes. The authors recognize that sleep time and quality of sleep are hard to measure by employing a simple questionnaire.

The main data results on seizure trigger factors are presented in figure 2.

In conclusion, there is strong evidence of an influence of sleep homeostatic mechanisms on central circadian clock functioning that comes from sleep deprivation experiments, classically associated with induction of epileptic seizures and IEDs [7]. This effect is especially evident in primary generalized epilepsy, regardless of the sleep effect, this deprivation determines the slowing of brain waves and is a good marker of the homeostatic regulation of sleep. However, the question remains whether sleep deprivation has a genuine activating effect on IEDs or acts as a form of sleep induction, but when comparing it to drug-induced deprivation, there are more IEDs in the former [19]. According to Bartolini *et al*.[2], sleep deprivation is reported as a seizure precipitant by about two-thirds of PWEs, even just for one hour less than usual, mainly those with generalized epilepsies, particularly juvenile myoclonic epilepsy. However, as reported by these same authors, sleep deprivation seems less important in people with drug-resistant epilepsy who suffer daytime sleepiness, as they would be not as great prone to sleep deprivation.

Although nocturnal seizures can be an important part of insomnia, it could also be that a person has a sleep disorder made worse by epilepsy, in a bidirectional way. In this scenario, many PWEs is not getting the treatment they need for comorbid disorders, such as sleep disorder.

In conclusion, seizure triggers are often multiple and combined, but a loss of sleep stands out as an important one[26].

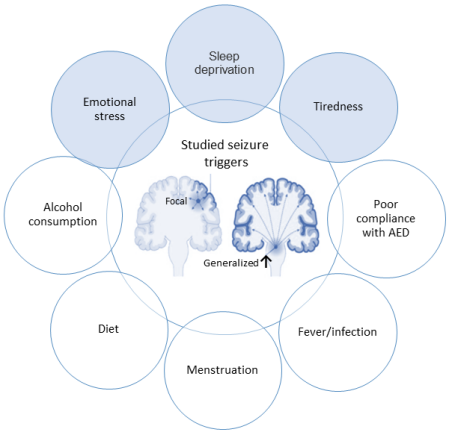

Figure 2. Seizure triggers. The main data of studies on seizure trigger factors are presented[2 12 26]. Anxiety and depression are especially common in PWEs whose seizures are worsened by emotional stress[2]. The generalized seizures, mainly genetics as the one more prone for seizures after sleep loss.

Insomnia and epilepsy, and related risk factors

In insomnia, there is general cognitive hypervigilance, a state of heightened arousal and learned sleep prevention from developing it with quality[33]. However, insomnia disorder despite being a major public health burden, its pathophysiology is not fully understood, but several etiological models have been proposed for explaining it, as neurobiological as well as psychological have been suggested highlighting genetic, behavioral, cognitive, emotional, and neurobiological factors[4].

As already mentioned, genetic factors also contribute to the regulation of sleep-wake characteristics, including the duration and timing of sleep, and there is evidence to suggest that several genes related to brain functioning, regulation of arousal and sleep-wake processes are associated with insomnia. The first studies conducted examined the role of circadian genes in the production of insomnia (eg, CLOCK and the Per genes)[25].

For explaining insomnia, there are many theoretical models relating to its etiology and pathophysiology, including the classic one of the Spielman model of insomnia, also known as the "Three Factor" or "Three P" model (predisposing, precipitating and perpetuating factors)[25]. Insomnia usually starts with a specific problem, which can last chronically caused by anxiety about sleep, maladaptive sleep habits and the possibility of an underlying vulnerability in sleep regulatory mechanisms, but the continuity of the precipitating stressor can also contribute, as well as physical or psychiatric comorbidity, especially anxiety and depression[33].

Ultimately, it is also recognized the combined and interlinked effects of physiological and psychosocial stress lead to emotional, cognitive , and physiological disorders [5] [10].

The aforementioned theories point to the influence of cognitive, emotional and physiological hyperexcitation in the development and maintenance of insomnia, and the hyperexcitation processes seem to play a fundamental role in its pathophysiology, as demonstrated by Feige *et al*.[8]. Autonomous, neuroendocrine, euroimmunological, electrophysiological, neuroimaging and psychological studies present evidence in this regard[8]. In addition, there is the concept of cognitive arousal that is central to models of sleep disturbance and insomnia, but the findings remain mixed if cognitive arousal is linked to objective sleep alterations and physiological hyperarousal.

Kalmbach *et al.*[17] studied nocturnal cognitive arousal measured by Presleep Arousal Scale Somatic factor. They found that high levels of nocturnal cognitive arousal were associated with prolonged sleep latency, lower sleep efficiency, and shorter total sleep time by PSG.

The neurobiological perspectives of the mentioned insomnia models particularly look at physiological alterations such as brain circuits that may be involved in its pathophysiology[4].

The vulnerability of functions to develop insomnia can be found in brain circuits that regulate emotion and arousal, rather than in the regulation of the circadian and homeostatic circuits of sleep[31]. Besides,people with chronic insomnia and restless REM sleep have interference on overnight adaptation in the limbic circuit of the brain for resolving the burden of emotional memories by making them milder and more tractable. Also,restless REM sleep has insufficient noradrenergic silencing[31].

Some longitudinal studies have confirmed that persistent insomnia is associated with a dramatic increase in the risk of developing psychiatric disorders, with insomniacs demonstrating a high level of daytime arousal on various neurophysiological measures. Furthermore, stress has been suggested to be a trigger for seizures in PWEs. A systematic review by Cano-López *et al*.[5] 5 summarizes the evidence on this topic. Following PRISMA guidelines, 38 articles were selected, 14 analyzing basal cortisol levels, eight, the effects of AEDs, 13 focusing on the effects of seizures, and three examining stress. As a result, higher basal cortisol levels were found in patients than in healthy people in studies with the most homogeneous samples (45% of the total of 38 studies). Despite the heterogeneous results associated with AEDs, seizures were related to increases in cortisol levels in 77% of the total of 38 studies. The only study with acute stress management found greater cortisol reactivity in PWEs than in healthy controls.—

In studies that used self-reported stress, high seizure frequency was related to increased levels of cortisol and less functional brain connectivity. The results suggest that epilepsy can be considered a model of chronic stress[5] [10], and it seems likely that changes in the excitability of the network may result in or contribute to increased susceptibility to seizures resulting from non-linear interactions between cortisol levels and other stress mediators[5].

It should be noted from the outset thatinsomnia was considered a "psychophysiological" disorder with crucial involvement of mental and behavioral factors that play a role, whether predisposing, precipitating, or perpetuating[33]. In addition, psychiatric and neurological comorbidities are relatively frequent in PWEs, affecting on average between 30 and 50% of them, and several population-based studies have suggested that primary depression increases the risk of developing epilepsy by twice and suicide by three to four times. Besides, a mood disorder preceding the onset of epilepsy has been associated with an increased risk of developing treatment-resistant epilepsy[18]. But as stated by Yang *et al*.[34], in PWEs, it appears that the severity of insomnia is more likely to be associated with comorbid medical and depressive symptoms, but less likely to be directly related to epilepsy. However, further research is needed regarding this complex and multilevel subject. In summary, it appears that insomnia in PWEs has a complex interaction between psychosocial stress, its mediators and mental disorders [figure 3].

The physiological hyperarousal is associated with short sleep duration in insomnia and the activation of both arms of the stress system, the hypothalamic-pituitary-adrenal (HPA) axis and the sympatho-adreno-medullary (SAM). Many individuals who experience chronic sleep deprivation and circadian rhythm disruption modify the release of cortisol regulated by the HPA axis. In particular, the release of adrenocorticotropin (ACTH) into the blood is under circadian control, resulting in high levels of cortisol being secreted just prior and during the active part of the day, with lower levels of release towards evening and sleep, and also, there is an ultradian rhythm of ACTH release. Consequently, the release of cortisol helps adjust and 'fine-tune' metabolic and immune responses to the diverse needs of activity and sleep, but when there is sleep disruption and other stressors, the HPA is activated ensuing in high levels of cortisol. Also, sleep deprivation activates the SAM drive, which, via the sympathetic nervous system, stimulates the release of catecholamines, mainly epinephrine/adrenaline, from the adrenal medulla[10]. Consequently, many of these individuals have increased secretion of adrenocorticotropic hormone and cortisol compared to healthy individuals, although patients with insomnia have normal circadian secretion patterns of these hormones, their levels are elevated during the night and in the first half of the night[25].

Besides, regarding measures of metabolic rate such as body temperature, heart rate, electroencephalographic activity, catecholamines, and oxygen consumption, the systematic review by Chapman *et al*.[6] show that it appears to be increased across 24 h in line with the hyperarousal model of insomnia, however,it was minor compared to good-sleeping controls.

The counterpart, PWEs with stress-sensitive seizures present a noticeable brain response to stress hormones, and it seems that there is a positive correlation between cortisol levels and IEDs, but a negative correlation between it and global functional connectivity on EEG[2].

Besides, some insomnia models suggest that sleep state misperception in insomnia is related to the increased sensory and information processing during NREM sleep[23]. Regarding the REM sleep instability hypothesis, the subjective experience of insomnia would be related to decreased REM sleep per cent and increased REM EEG arousals. There is also, as already mentioned, a heightened CAP rate – a non-REM sleep EEG marker of unstable sleep and poor sleep quality, a sleep-wake state amalgam[4]. Zhao *et al.*[36] presented in their systematic review about EEG spectral analysis in insomnia disorder that patients presented: during wakefulness and sleep, increased beta-band power, that sometimes spread into neighbouring frequency bands; during wakefulness, increased theta and gamma power; during REM sleep, increased alpha and sigma power; besides decreased delta power and increased theta, alpha, and sigma power during NREM sleep. In sum, it is postulated that insomnia occurs in association with heightened arousal or hyperarousal that may be seen as a preponderance of the arousal and wake-inducing brain pathways of the flip-flop switch.

Epileptic seizures are more likely to occur in NREM phases, most commonly seen at the time of sleep deprivation, however, the insomnia model is that of hyperarousability that does not favor wave brain deceleration, but has faster waves, in addition to more REM-tonic segment that may be made up of more epileptogenic elements. Another interesting coincidence is that sleep-related arousal disorders and hyper motor epilepsy may be related to increased levels of sleep instability, greater amounts of slow-wave sleep and NREM/REM sleep imbalance. As Mutti *et al.*[22] noted, their sleep texture is extremely similar, although the CAP metrics reveal quantitative differences, patients with hyper motor epilepsy show greater arousal instability compared to sleep-related arousal disorders. These facts deserve special reassessment, also about the link with insomnia, a hyperarousal disorder, and seizures.

The 'restless REM sleep indicates insufficient locus coeruleus silencing. It should be noted that "restless REM sleep" is supposedly a feature of several psychiatric disorders (such as insomnia, depression and anxiety disorders), and according to Simor *et al*.[29], patients with an insomnia disorder characterized by increased environmental alertness may change towards the tonic REM state. Moreover, a meta-analysis by Hertenstein *et al*.[15], provides more evidence that insomnia increases the risk for psychopathology and is a significant predictor for the onset of depression, anxiety, alcohol abuse and psychosis. Furthermore, the permanence of the precipitating stressor may also be a contributing factor, with some cases of insomnia being precipitated or comorbid besides with other psychiatric disorders, also physical illnesses[33].

The main features and the complex physiological interaction at various levels of epilepsy and insomnia are sketched in Figure 4.

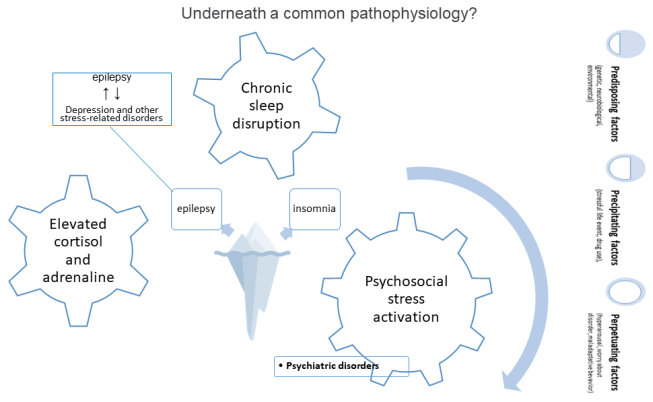

Figure 3. Complex relations among epilepsy, insomnia and psychiatric disorders. The suggestion of sharing of some common pathogenic mechanisms. Insomnia increases the risk for psychopathology, and psychophysiological insomnia and epilepsy have increased cortisol. Besides, it is well known the bidirectional relationship between mood disorders and epilepsy[2 5 10 15 18 33]

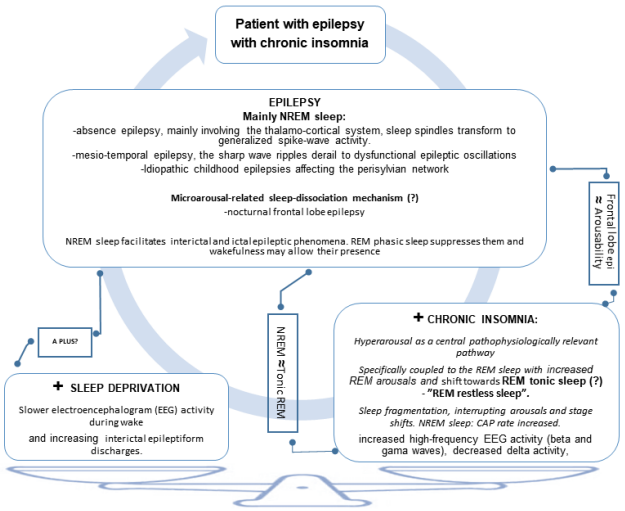

Figure 4. Complex multilevel interaction of epilepsy and insomnia. The known relationship between seizure and sleep triggers, such as sleep deprivation, besides the less known one as insomnia with cortical hyperarousability in its "insomnia neurosciences" beginning. It is hypothesized here that the role of increased arousability in insomnia may be related to the propensity to seizure in PWEs, as supposedly occur in frontal lobe epilepsy [3 14 19 22 28 29 31 36]

CONCLUSIONS

There is a complex relationship between insomnia and epilepsy, but further study should unveil the contribution of insomnia to the presentation of seizures, when different factors, such as mood problems and environmental factors, also play a role. Future studies should also aim to compare patients with different types of seizures and look for a common pattern in sleep architecture, and also assess the role of hypnotics in improving insomnia by increasing the level of slow-wave sleep and their role in causing seizures.

Given the potential therapeutic benefits of treating sleep disorders in seizure control, routine screening of insomnia symptoms is recommended, including investigation of the connection between epilepsy triggers and insomnia with preventive therapeutic goals. Besides, as the recognized interlink between mood and anxiety disorders with insomnia, it would be advised to take special care of the management of psychiatric comorbidities of the PWEs.

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