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Seizure Timing and Circadian Patterns: A Comprehensive Bibliographic Review

Cronometragem das Crises Epilépticas e Padrões Circadianos: Uma Revisão Bibliográfica Abrangente

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ABSTRACT

Epilepsy's cyclic nature, increasingly quantified through advancements in continuous electroencephalography (cEEG), reveals robust seizure cycles including circadian, multidien, and circannual rhythms. Understanding these cycles' mechanisms and clinical implications, such as seizure forecasting and optimized treatment timing, is crucial. Despite historical observations, detailed analysis of seizure timing cycles has become feasible only recently, necessitating further research to confirm generalizability and clinical relevance.

This paper reviews current literature on circadian rhythms in epilepsy, focusing on temporal seizure patterns and identifying knowledge gaps. A comprehensive review of studies, primarily using PubMed, synthesizes key findings from 20 studies on the temporal dynamics of epileptic activity.

Research shows consistent circadian rhythms in seizure activity, with distinct daily peaks. Seizures often follow daily patterns, termed "seizure rush hours," with specific seizure types linked to particular times and influenced by sleep-wake cycles. These findings underscore the importance of understanding temporal patterns in epilepsy.

Understanding these rhythms can enhance seizure prediction, diagnosis, and personalized treatment strategies. The significant role of biological rhythms suggests that tailored treatments based on individual circadian profiles could improve patient outcomes and quality of life. Further research is essential to elucidate the mechanisms driving these influences and validate findings across diverse cohorts.

Keywords: epilepsy, circadian rhythms, seizure patterns, chronotherapy

RESUMO

A natureza cíclica da epilepsia, cada vez mais quantificada por meio dos avanços na eletroencefalografia contínua (cEEG), revela ciclos de crises epilépticas (CE) robustos, incluindo ritmos circadianos, multidiários e circanuais. Compreender os mecanismos e as implicações clínicas desses ciclos, como a previsão de CE e a otimização do momento do tratamento, é crucial. Apesar das observações históricas, a análise detalhada dos ciclos de tempo das CE tornou-se viável apenas recentemente, exigindo mais pesquisas para confirmar a generalização e a relevância clínica.

Este artigo revisa a literatura atual sobre ritmos circadianos na epilepsia, focando nos padrões temporais das CE e identificando lacunas no conhecimento. Uma revisão abrangente dos estudos, principalmente utilizando o PubMed, sintetiza os principais achados de 20 estudos sobre a dinâmica temporal da atividade epiléptica.

A pesquisa mostra ritmos circadianos consistentes na atividade das CE, com picos diários distintos. As CE frequentemente seguem padrões diários, denominados "horários de pico das convulsões" ("seizure rush hours"), com tipos específicos de CE vinculados a determinados horários e influenciados pelos ciclos sono-vigília. Esses achados destacam a importância de entender os padrões temporais na epilepsia.

Compreender esses ritmos pode melhorar a previsão, o diagnóstico e as estratégias de tratamento personalizado das CE. O papel significativo dos ritmos biológicos sugere que tratamentos personalizados com base nos perfis circadianos individuais podem melhorar os resultados e a qualidade de vida dos pacientes. Mais pesquisas são essenciais para elucidar os mecanismos que impulsionam essas influências e validar os achados em diversas coortes.

Palavras-chave: epilepsia, ritmos circadianos, padrões de convulsões, cronoterapia

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INTRODUCTION

Epilepsy is characterized by its cyclic nature, a phenomenon recognized for centuries but increasingly quantified with recent technological advancements enabling precise measurement of seizure cycles across different timescales[1]. Longitudinal studies utilizing continuous electroencephalography (cEEG) have confirmed robust seizure cycles, including circadian, multidien, and circannual rhythms, significantly influencing periods of heightened seizure susceptibility. Understanding these mechanisms and their clinical implications, such as seizure forecasting and optimized treatment timing, represents a crucial area of current epilepsy research. The evolving understanding of epilepsy's temporal dynamics holds promise for enhancing patient care, necessitating ongoing investigation.

Despite early anecdotal clinical observations of cyclical seizures dating back to Gowers in 1881 and more extensive studies by Griffiths and Fox in 1938, rigorous analysis of seizure timing cycles has only recently become feasible due to technological limitations[2]. Early studies relied on inpatient seizure monitoring and seizure diaries, while recent advancements in cEEG have enabled more accurate and extended observations of seizure cycles. Studies utilizing data from NeuroVista and NeuroPace have identified cyclical patterns in interictal epileptiform discharges (IED) and electrographic seizures; however, the generalizability and clinical relevance of these findings remain to be fully elucidated, particularly with larger and longer-term studies incorporating patient-reported seizures.

Epilepsy, affecting 65 million people globally, primarily manifests through seizures arising from disruptions in neuronal excitability regulation. These disruptions, observed at various scales from cellular paroxysmal depolarization shifts to macroscopic epileptiform discharges (EDs) in EEG, are increasingly recognized for their rhythmicity. Recent studies indicate that EDs exhibit cycles across ultradian, circadian, and multidien rhythms, yet the physiological mechanisms governing these rhythms and their modulation by intrinsic and extrinsic factors are not fully understood, which limits their clinical application[3].

The bidirectional relationship between sleep, circadian rhythms, and epilepsy in adults underscores the heightened prevalence of disrupted sleep-wake cycles among individuals with epilepsy compared to the general population[4]. Over 90% of individuals with epilepsy experience seizures that follow circadian periodicity, particularly during sleep, highlighting the intricate interplay between sleep-related epilepsy and the body's internal clock. It is important to note that this review does not focus on chronotype, which is the subject of another author's paper titled "Chronotype Variability in Epilepsy and Clinical Significance: Scoping Review"[5]. While this paper explores the rhythmicity of seizures, the other examines the sleep-wake cycle patterns in patients with epilepsy. Insights gained could lead to enhanced diagnostic methods and tailored treatment strategies based on individual circadian profiles, potentially improving patient outcomes and quality of life.

This paper reviews the current literature on circadian rhythms and epilepsy, focusing on temporal seizure patterns associated with circadian cycles and identifying gaps in understanding that necessitate further investigation. The paper proceeds with an exploration of key findings from 20 selected studies (Tables 1 and 2), aiming to provide comprehensive insights into the temporal dynamics of epileptic activity influenced by circadian rhythms.

BIBLIOGRAPHIC SEARCH METHODOLOGY

A thorough search was performed on PubMed using the terms circadian, seizure*, epilep*, pattern, and rhythm*, limited to title and abstract, with no other restrictions, yielding a total of 443 papers.

The titles and abstracts of these papers were screened for relevance. Studies were included if they provided empirical data on circadian patterns of epileptiform discharges or seizure occurrence, leading to the selection of 17 papers for full-text review.

In addition to the database search, a manual search identified three additional relevant studies by Schroeder et al. 2020[6], Leguia et al. 2021[2], and Nzwalo et al. 2016[7].

Ultimately, 20 studies were included in this review on circadian rhythms and epilepsy.

Inclusion criteria focused on observational studies involving patients with epilepsy that investigated circadian rhythmicity. Studies were excluded if they were reviews, conducted solely on animal models, or focused exclusively on chronotype.

RESULTS

Study and sample characteristics

Of the included studies (Tables 1 and 2), most focused on adult populations – 14/20. These studies examined the influence of circadian rhythms and sleep-wake cycles on seizure occurrence using various methods such as continuous intracranial EEG monitoring, seizure diaries, and electrocorticography monitoring systems. In adults, robust circadian and multidien seizure rhythms were observed, with specific variations depending on the epileptic focus location. Temporal and frontal lobe seizures followed distinct diurnal patterns influenced by circadian rhythms. Additionally, multidien cycles affecting seizure periodicity were identified. In pediatric studies, seizures exhibited well-defined circadian and sleep-wake patterns, with variations depending on seizure type and epileptic focus location. Generalized and frontal lobe seizures predominantly occurred during sleep and at night, while temporal lobe seizures were more frequent during wakefulness and the daytime. In both age groups, circadian patterns and sleep-wake states were crucial in determining seizure occurrence and periodicity.

Adult patients

Baud et al.[8] found that IED fluctuates with multidimensional circadian rhythms, typically lasting 20 to 30 days, and remaining relatively stable for up to 10 years in both men and women[8]. The study analyzed IED using wavelet transform to uncover circadian and multidien rhythms. Individual subjects exhibited clear circadian variation and longer multidien rhythms in IED. Spectral decomposition identified peaks at ultradian (12 h) and circadian (24 h) rhythms, as well as periodicities of 5.5–33 days. Subjects demonstrated strong intra-subject stability of these rhythms across different brain regions. Seizure timing correlated significantly with circadian and multidien IED phases, suggesting seizures are coupled to these rhythms. The risk of seizure occurrence varied by circadian and multidien phase, with the highest risk found when these rhythms were combined. This discovery may serve as a new biomarker for determining the relative risk of seizures[8].

In Schroeder et al., the observed temporal associations of seizure dissimilarities reflected gradual changes in seizure network evolutions across the length of each recording, indicating slow shifts in seizure pathways over multiple days[6]. Additionally, a positive correlation was identified between seizure dissimilarities and temporal distances at shorter timescales, which decreased at longer timescales. It was hypothesized that seizure pathways may change on shorter timescales, such as circadian rhythms, creating timescale-dependent relationships between seizures[6].

Specific seizure types are associated with particular times of the day. For instance, Karafin et al. (2010) identified a bimodal pattern of human epileptic seizures in mesial temporal lobe epilepsy (mTLE), with peak seizure frequencies occurring at 6-8 a.m. and 3-5 p.m., confirmed by generalized estimating equations analysis ($p<0.0001$ and $p<0.01$)9. This study reviewed epilepsy data from 60 patients, with a male-to-female ratio of 2:1. There were 34 left and 26 right temporal lobe seizure foci. Ages were similar: females 35.2 and males 37.3 years. A total of 694 seizures were recorded. And these circadian patterns observed were consistent across demographics, with the afternoon peak notably influenced by females and those aged 30-39[9].

Anderson et al. examined 65 patients with focal onset seizures to characterize cyclic diurnal and nocturnal patterns of electrocorticographic IED10. Hourly detection rates of ED showed significant circadian periodicity in 97% of patients, with peaks generally between 11 p.m. and 5 a.m., and minor peaks in the early afternoon. Statistically significant circadian rhythms were observed in most lobe-by-detection type categories, except for theta band ED in the temporal lobe and alpha band ED in the occipital lobe[10].

Spencer et al. recognized that circadian and ultradian patterns of EDs differ depending on the location of seizure onset[11]. This study analyzed 84-day intracranial recordings in patients with epilepsy, showing a steady circadian rhythm in EDs, with a strong 24-hour periodicity. Long episodes were validated as seizures in 42% to 47% of cases across different brain regions. Cosinor analysis revealed a consistent acrophase for detections around 2 a.m. and 3 a.m., regardless of seizure onset region. However, long episodes in temporal neocortical and frontal regions peaked between 2 a.m. and 5 a.m., while those in mesial temporal regions peaked in the early evening. Individual analysis showed most subjects had robust 24-hour cycles of detections, often with additional 12-hour ultradian rhythms, varying by brain region[11].

Further, different epilepsy types and seizure localizations exhibit distinct patterns. Nzwalo et al. found non-uniform 24-hour seizure patterns in patients with refractory focal epilepsy, with a bimodal distribution in TLE, with seizure peaks between 10 a.m. – 1 p.m. and 4 p.m. – 7 p.m.[7]. This study involved 123 adults with focal epilepsy, investigating circadian patterns of seizures. No specific circadian pattern was observed in patients with extratemporal epilepsy. The majority of patients became seizure-free after surgery, irrespective of epilepsy duration, etiology, or sociodemographic factors[7].

Pavlova et al. showed that frontal lobe seizures peaked between midnight and noon, around 6:30 a.m., while temporal lobe seizures peaked from noon to midnight, indicating distinct day/night patterns[12]. This study analyzed 831 reports with a mean age of 46 years. It identified 129 electrographic seizures from 44 patients, primarily in the frontal (31) and temporal (71) lobes. Non-seizure symptoms included 1956 complaints, with nocturnal motor events and sensory complaints being the most frequent[12].

Leguia et al.[2] revealed significant findings on seizure cycles across different timescales, temporal patterns of seizures, and preferred timing of electrographic seizures. The study found that in 222 adults with refractory focal epilepsy, cEEG and seizure diaries indicated five daily peaks and multidien cycles with periodicities of 7, 15, 20, and 30 days, showing variability in seizure timing. Specifically, 89% of patients exhibited circadian seizure cycles, with electrographic seizures peaking around 6 p.m., while 60% displayed multidien cycles, approximately 7-day and 30-day, and 12% had circannual cycles with a spring peak. Both electrographic and self-reported seizures showed a tendency to occur during the rising phases of multidien IED cycles, indicating a close association between seizures and IED fluctuations. Additionally, while some patients demonstrated seasonal seizure preferences, there was no consistent group trend[2].

Cheng et al. examined the influence of circadian rhythms on the incidence of status epilepticus (SE) in critically ill patients, analyzing data from 4413 patients[13]. The study found significant differences in circadian rhythms of body temperature, blood oxygen saturation, and heart rate between SE and non-SE groups. Machine learning algorithms identified ten significant variables and developed a predictive model. The findings indicated a higher risk of SE during late night to early morning hours, suggesting increased monitoring during these times[13].

Fukuda et al. compared circadian rhythms and profiles between patients with juvenile myoclonic epilepsy (JME) and TLE[14]. Among 16 JME and 37 TLE patients, 87% of JME patients and 59% of TLE patients reported sleeping after seizures. Fewer JME patients felt better before 10:00 AM compared to TLE patients. The study concluded that while no distinct circadian profile differentiated JME from TLE, JME patients generally felt less optimal early in the day[14].

Hofstra et al. conducted studies on the influence of circadian rhythms on seizure occurrence using long-term EEG and video monitoring. In a pilot study with 21 patients, they found that temporal lobe seizures occurred mainly between 11 a.m. and 5 p.m., while frontal lobe seizures were most frequent between 11 p.m. and 5 a.m.. Seizure timing correlated with the individual's circadian phase, measured by dim light melatonin onset (DLMO); temporal seizures peaked in the 6 hours before DLMO, and frontal seizures in the 6-12 hours after DLMO, suggesting synchronization with the circadian timing system[15]. In a subsequent study with 33 patients, including many from the pilot study, they observed similar diurnal patterns among 450 seizures. Temporal lobe seizures were most frequent between 11 a.m. and 5 p.m., frontal seizures between 11 p.m. and 5 a.m., and parietal seizures between 5 p.m. and 11 p.m.. Awake state seizures peaked between 5 a.m. – 11 a.m. and 5 p.m. – 11 p.m., while sleep state seizures peaked between 11 a.m. – 5 p.m. and 11 p.m. – 5 a.m., highlighting strong diurnal patterns based on seizure origin and behavioral state [15-16] .

Pavlova et al. analyzed day/night seizure patterns in 15 patients with TLE and 11 with extratemporal lobe epilepsy (XTLE) using video-EEG recordings[17]. In TLE, 50% of seizures occurred between 3 p.m. and 7 p.m., whereas XTLE seizures peaked between 7 p.m. and 11 p.m.. Fewer seizures in TLE occurred during sleep (19%) compared to XTLE (41%). The study concluded that both circadian rhythms and sleep/wake state influence seizure occurrence, with distinct patterns depending on the epileptogenic region[17].

In the NeuroVista study by Karoly et al, data from 12 patients (8 men, 4 women) revealed significant 24-hour rhythms in seizure occurrence, with patient 8 demonstrating a stronger 12-hour cycle18. Patients 1, 7, and 4 also exhibited cycles of approximately 1 week or 2 weeks. SeizureTracker data from 1118 patients confirmed circadian seizure patterns and weekly cycles, with some showing longer periodicities up to a month. Clustering analysis indicated that 40% of seizures occurred in clusters, affecting cycle assessment. Overall, at least 86% of patients showed significant seizure cycles, primarily circadian (80%) with peaks at breakfast and dinner. Weekly cycles were evident in 7% (Monte-Carlo) to 21% (Hodges-Ajne) of patients, with some showing cycles longer than 3 weeks. Notably, seizure types and epilepsy syndromes did not differ significantly across patients with different cycle durations[18].

Pediatric patients

The influence of sleep-wake cycles is significant in epilepsy. Zarowski et al. highlighted that tonic and tonic-clonic seizures are more frequent during sleep in generalized seizures, whereas other types of generalized semiological seizures occur more frequently during wakefulness[19]. A total of 230 (73%) seizures occurred during wakefulness and 86 (27%) during sleep ($p < 0.001$). Daytime had 62% of seizures, nighttime 38% ($p < 0.001$). Idiopathic generalized epilepsy had more wakefulness seizures, whereas symptomatic generalized epilepsy had more sleep seizures. Clonic, tonic, and tonic–clonic seizures peaked 6-9 a.m.; absence 9 a.m.-noon and 9 p.m.-midnight; atonic noon-6 p.m.; myoclonic 6 a.m.-noon. Epileptic spasms peaked 6-9 a.m. and 3-6 p.m. during wakefulness[19].

Loddenkemper et al. evaluated the relationship between sleep/wake and day/night patterns with various subtypes of epileptic seizures and locations of epilepsy, finding that sleep-wake patterns are reliable predictors of seizure semiology and localization[20]. Patient data from 225 individuals (113 female) and 1008 seizures were analyzed. Multinomial logistic models confirmed sleep/wakefulness as a better predictor, with lower residual deviance (4,804 vs. 4,922). Seizure types like auras and gelastic occurred more in wakefulness, while tonic-clonic and automotor seizures were more frequent during sleep. Generalized seizures were more common in wakefulness and daytime, while frontal seizures occurred predominantly in sleep and at night[20].

Ramgopal et al. showed that generalized tonic-clonic evolution in pediatric patients is influenced by sleep-wake cycles and time of day[21]. This study analyzed 3-hour time blocks and found tonic–clonic evolutions most frequent between 12 a.m.–3 a.m. and 6 a.m.–9 a.m. ($p < 0.05$), predominantly during sleep ($p < 0.001$). Patients with generalized EEG seizure onset showed more tonic–clonic evolutions between 9 a.m.–12 p.m. ($p < 0.05$), while those with focal EEG onsets generalized between 12 a.m.–3 a.m. and 6 a.m.–9 a.m. ($p < 0.05$), often out of sleep ($p < 0.001$). Secondary generalizations in temporal lobe seizures peaked between 3 a.m.–6 a.m. ($p < 0.05$) and in extratemporal lobe seizures between 12 a.m.–9 a.m. out of sleep ($p < 0.001$). Magnetic resonance imaging lesions correlated with more tonic–clonic evolutions between 12 a.m.–6 a.m. and 6 a.m.–9 a.m. out of sleep ($p < 0.01$, $p < 0.05$)[21].

Gurkas et al. investigated the sleep/wake cycle and 24-hour periodicity of various seizure subtypes in 170 pediatric epilepsy patients[22]. Video-EEG monitoring of 909 seizures revealed specific patterns: auras, dialeptic, myoclonic, hypomotor, atonic seizures, and epileptic spasms were more frequent during wakefulness, while tonic, clonic, and hypermotor seizures were more frequent during sleep. Temporal lobe seizures occurred mostly during wakefulness, whereas frontal lobe seizures occurred predominantly during sleep. The study concluded that seizure occurrence in children follows specific circadian patterns depending on the seizure type and localization[22].

Ramgopal et al. analyzed 1754 seizures in 390 pediatric patients using video-EEG monitoring[23]. Generalized seizures were more common during wakefulness and daytime, while seizure occurrence at night increased with age. Temporal lobe seizures were more frequent during wakefulness, and frontal lobe seizures occurred more during sleep in adolescents. The study suggested that circadian rhythmicity changes with age, affecting seizure susceptibility and helping predict periods of high seizure propensity[23].

Nagao et al. studied twelve pediatric patients with typical absence seizures to investigate the circadian rhythm of 3 Hz spike wave complex using video-EEG with telemetry[24]. They found that s-w paroxysms, combined with clinical symptoms and lasting more than four seconds, were fewer in the afternoon compared to the morning and during sleep. The correlation ratio between the frequency and duration of s-w paroxysms was statistically significant ($r = -0.74$, $p < 0.02$). S-w paroxysms were shorter and deformed during sleep, highlighting the importance of morning observations for typical absence seizures. Electroencephalographic recordings with sufficient stimulation, such as hyperventilation, are crucial for patients with modified s-w paroxysms during sleep[24].

Table 1. Studies about biological rhythms in adult patients with epilepsy.

Study	Population/Design	Evaluation	Main Findings	Conclusions
Leguia et al., 2021, Switzerland [2]	222 adults with refractory focal epilepsy / Retrospective cohort study	Continuous intracranial EEG (cEEG) and seizure diaries	Seizures peaked at five times throughout the day; multidien cycles with peaks at 7, 15, 20, and 30 days	Seizure timing varies significantly
Schroeder et al., 2020, UK [6]	31 patients with focal epilepsy / Retrospective study	Continuous intracranial EEG recordings	Seizure paths changed on circadian or slower timescales and were independent of medication reduction	Seizure pathways are influenced by timescale-dependent processes
Baud et al., 2018, USA [8]	37 patients with epilepsy / Retrospective study	NeuroPace RNS® System; intracranial leads	Circadian and multidien rhythms influence seizures, with higher risk during combined critical phases	Combined circadian and multidien rhythms can predict seizure risk
Karoly et al., 2018, Australia [18]	1128 patients / Retrospective study	Continuous electrocorticography monitoring	92% of seizures showed circadian patterns; 7-21% weekly patterns	Seizure activity is influenced by multiday cycles, including circadian and weekly rhythms
Spencer et al., 2016, USA [11]	134 adults with intractable focal epilepsy / Retrospective study	NeuroPace RNS System	Strong circadian patterns with regional variations in long episodes	Nocturnal circadian influence on brief discharges varies by brain region
Nzwalo et al., 2016, Portugal [7]	123 patients with refractory focal epilepsy / Retrospective study	Video-EEG monitoring	Temporal lobe epilepsy showed bimodal circadian patterns; no specific patterns in extratemporal epilepsy	Seizure distribution shows temporal and neocortical patterns in refractory epilepsy
Anderson et al., 2015, USA [10]	65 subjects with focal onset seizures / Retrospective study	RNS System	97% showed circadian periodicity, peaking between 11 PM and 5 AM	Majority of patients exhibit circadian patterns in epileptiform discharges
Pavlova et al., 2012, USA [12]	831 ambulatory EEG reports / Retrospective study	Ambulatory EEG using DigitraceTM	Frontal lobe seizures peaked between midnight and noon; temporal lobe seizures peaked between noon and midnight	Day/night seizure patterns vary by lobe
Karafin et al., 2010, USA [9]	60 patients with refractory mesial temporal lobe epilepsy / Retrospective study	Video-EEG monitoring	Peak seizures occurred at 6-8 a.m. and 3-5 p.m.	Mesial temporal lobe epilepsy shows morning and afternoon seizure peaks
Cheng et al., 2024, China [13]	4413 critically ill patients / Retrospective study	Diurnal rhythm analysis of vital signs using machine learning	Significant circadian rhythm differences in vital signs between SE and non-SE groups	Increased monitoring and intervention recommended during late night to early morning to reduce SE risk
Hofstra et al., 2011, Netherlands [15]	21 patients / Prospective pilot study	Dim light melatonin onset (DLMO)	Temporal lobe seizures mainly between 11:00 and 17:00, frontal seizures between 23:00 and 05:00	Seizure timing is synchronized to the circadian system
Fukuda et al., 2015, Brazil [14]	53 patients (JME and TLE) / Retrospective study	Sleep-wake cycle and circadian profile questionnaire	87% of JME patients and 59% of TLE patients slept after seizures; 19% of JME patients felt better before 10:00 AM	No clear distinct circadian profile between JME and TLE patients
Hofstra et al., 2009, Netherlands [16]	33 patients / Observational study	Intracranial EEG monitoring	Temporal lobe seizures preferentially between 11:00 and 17:00; frontal seizures between 23:00 and 05:00; parietal seizures between 17:00 and 23:00	Seizures show strong diurnal patterns based on origin and state
Pavlova et al., 2004, USA [17]	26 patients (TLE and XTLE) / Observational study	Video-EEG recordings	TLE seizures peaked between 15:00 and 19:00; XTLE seizures peaked between 19:00 and 23:00	Seizures exhibit clear day/night patterns, varying by epileptogenic region

EEG: Electroencephalogram, JME: juvenile myoclonic epilepsy, SE: status epilepticus, TLE: temporo-lobe epilepsy; XTLE: extra temporo-lobe epilepsy.

Table 2. Studies about biological rhythms in pediatric patients with epilepsy

Study	Population/Design	Evaluation	Main Findings	Conclusions
Zarowski et al., 2011, USA [19]	77 children with generalized seizures / Retrospective study	Video-EEG monitoring	Clonic and tonic-clonic seizures peaked from 6-9 a.m.; absence seizures peaked from 9 a.m.-noon and 9 p.m.-midnight	Circadian and sleep-wake patterns are crucial for guiding diagnostics and therapy
Loddenkemper et al., 2011, USA [20]	225 pediatric patients / Retrospective study	Video-EEG monitoring	Generalized seizures occurred more during wakefulness and daytime; frontal seizures during sleep and at night	Sleep, wakefulness, and day-night cycles are critical for understanding seizure types and localization
Ramgopal et al., 2012, USA [21]	71 patients / Retrospective study	Video-EEG monitoring, seizure localization, MRI	Tonic-clonic evolutions peaked at 12-3 AM and 6-9 AM, with more evolutions during sleep	Time of day and arousal state influence pediatric tonic-clonic seizures
Gurkas et al., 2016, Turkey [22]	170 pediatric patients / Retrospective study	Video-EEG monitoring	Seizures showed distinct patterns based on wakefulness vs. sleep, and day vs. night	Seizures in children occur in specific circadian patterns and sleep/wake distributions based on onset location and semiology.
Ramgopal et al., 2014, USA [23]	390 pediatric patients / Retrospective study	Video-EEG monitoring during tapered drug withdrawal	Generalized seizures more common during wakefulness and daytime; nighttime seizures increased with age	Circadian rhythmicity changes alter seizure susceptibility in different age groups
Nagao et al., 1990, Japan [24]	12 pediatric patients / Observational study	Video-EEG with telemetry	Fewer S-W paroxysms in the afternoon than in the morning and during sleep	Morning observations of absence seizures are critical, and sufficient EEG recording with stimulation is essential for modified S-W during sleep

EEG: Electroencephalogram, MRI: Magnetic resonance imaging, S-W: Spike-and-Wave paroxysms.

DISCUSSION

Adult patients

The adult studies on epilepsy and circadian rhythms have yielded several significant insights. Firstly, many studies have demonstrated a strong association between specific seizure types and distinct circadian patterns. For instance, Schroeder et al.[6] identified temporal associations in seizure dissimilarities, reflecting slow shifts in seizure pathways over multiple days. Additionally, Karafin et al.[9] and Spencer et al.[11] both highlighted the presence of bimodal and circadian patterns in seizure frequencies, with peaks occurring at various times of the day and night, depending on the seizure type and brain region involved. This suggests a robust underlying circadian influence on seizure occurrence.

Moreover, the studies underscore the importance of considering individual circadian rhythms in managing epilepsy. Baud et al.[8] found that IED fluctuates with multidimensional circadian rhythms, indicating that seizure risk is significantly influenced by these rhythms. Similarly, Anderson et al.[10] and Leguia et al.[2] reported that seizures and ED exhibit strong circadian periodicities, with specific times of higher seizure risk. This emphasizes the potential for using circadian patterns as biomarkers to predict and manage seizure occurrence more effectively.

The differentiation of TLE from frontal lobe epilepsy by timing is evident, with temporal lobe seizures typically peaking during the day, particularly in the afternoon, and frontal lobe seizures more common at night. These findings highlight the importance of considering circadian rhythms in epilepsy management, as they influence seizure occurrence and the optimal timing of interventions.

Karafin et al. identified a bimodal pattern in mTLE, with peak frequencies at 6-8 a.m. and 3-5 p.m. ($p<0.0001$ and $p<0.01$)[9]. Anderson et al. observed peaks in ED between 11 p.m. and 5 a.m., emphasizing distinct circadian rhythms in TLE[10]. Hofstra et al. confirmed that temporal lobe seizures peaked between 11 a.m. – 5 p.m., while frontal lobe seizures were most frequent between 11 p.m. – 5 a.m.[15-16].

Spencer et al. showed a 24-hour periodicity in discharges, with a consistent acrophase around 2-3 a.m., and long episodes in mesial temporal regions peaking in the early evening[11]. Pavlova et al. found that frontal lobe seizures peaked around 6:30 a.m., whereas temporal lobe seizures peaked from noon to midnight, indicating distinct day/night patterns[12].

Nzwalo et al. observed a bimodal distribution in TLE with peaks between 10 a.m. – 1 p.m. and 4-7 p.m., contrasting with the lack of specific circadian patterns in extratemporal epilepsy[7]. Fukuda et al. reported different profiles for JME and TLE, with fewer TLE patients feeling optimal early in the day[14].

Pediatric patients

Pediatric studies on epilepsy and circadian rhythms have revealed patterns that closely mirror those observed in adults, providing valuable insights into the relationship between seizure occurrence and biological rhythms across different age groups. Several studies have highlighted distinct circadian patterns in seizure types and their evolution in children. For example, Gurkas et al. (2016) found that different seizure subtypes exhibit specific temporal preferences, with auras, myoclonic, and atonic seizures more frequent during wakefulness, and tonic, clonic, and hypermotor seizures more common during sleep. This suggests a strong influence of sleep-wake cycles on seizure expression in pediatric epilepsy.

Furthermore, Ramgopal et al.[21, 23] demonstrated age related changes in circadian rhythmicity and seizure susceptibility. Generalized seizures were shown to be more prevalent during wakefulness and daytime in younger children, whereas the occurrence of seizures at night increased with age. Moreover, the timing of seizures varied by epilepsy type and seizure onset location, indicating differential circadian influences across different pediatric populations.

Lastly, these findings reveal that the influence of sleep-wake cycles on seizure occurrence is substantial. Studies by Zarowski et al.[19] and Loddenkemper et al.20 have shown that certain types of seizures, such as tonic-clonic and tonic seizures, are more likely to occur during sleep, while others, like auras and gelastic seizures, are more frequent during wakefulness. This aligns with Ramgopal et al.[21, 23], who demonstrated that generalized seizures tend to occur more during wakefulness and daytime, while focal seizures, particularly in the frontal lobe, are more prevalent during sleep. These observations highlight the necessity of incorporating sleep-wake cycles into the assessment and treatment plans for patients with epilepsy.

New therapies

Epilepsy research has illuminated the temporal dynamics of seizures, highlighting their periodic nature and the significant influence of circadian rhythms on seizure occurrence. Advances in diagnostic technology, including chronic intracranial EEG records, have confirmed the clinical observation of different temporal patterns of epileptic activity and seizures over 24 hours. This understanding has been pivotal in refining diagnostic criteria, classifying epilepsy syndromes, and developing personalized treatment strategies.

The analysis of various observations on the evolution and patterns of seizures in patients with focal epilepsy reveals a strong influence of circadian cycles and other slow-varying factors. Epileptic seizures and ED exhibit patterns significantly aligned with circadian rhythms, regardless of the seizure onset zone, but with varied patterns for longer bursts of discharges. Patients with refractory TLE show a bimodal pattern of seizure distribution over 24 hours, with specific peaks in the morning and afternoon. These circadian patterns and robust cycles are consistent across a wide range of patients, irrespective of sex, suggesting that most epilepsies are influenced by the time of day. However, individual patient pattern analysis is crucial for providing quality treatments.

In ambulatory outpatient settings, seizures follow day/night patterns similar to those observed in inpatient conditions, with frontal seizures occurring preferentially in the early morning and temporal seizures in the early evening. These findings highlight the importance of considering circadian rhythms and specific temporal patterns when planning and adjusting epilepsy treatments.

These findings collectively highlight the complexity and importance of temporal patterns in epilepsy. Understanding the influence of circadian and multidien rhythms, as well as sleep-wake cycles, on seizure occurrences can inform personalized treatment strategies. This approach has the potential to improve patient outcomes by tailoring interventions to the temporal dynamics of epilepsy, including the use of chronotherapy and seizure forecasting.

The potential for enhancing seizure prediction algorithms through patient-specific modifications offers promising avenues for improving the quality of life and safety of epilepsy patients. Tailored treatment approaches, including personalized antiepileptic dosing regimens based on circadian phases, hold significant potential for enhancing seizure control and minimizing associated risks and side effects.

Advancements in diagnostic technology, particularly chronic intracranial EEG records, have provided valuable insights into the varied temporal patterns of epileptic activity over a 24-hour period. This knowledge is crucial for the development of targeted therapies and the evaluation of new treatment options.

Despite these advancements, challenges remain in accurately estimating seizure timings. The utilization of long-term wearable monitoring systems presents an opportunity for significant progress in understanding the natural history of epilepsy and refining treatment strategies.

Deep brain stimulation (DBS) targeting thalamic circuits could represent a novel therapeutic approach within the realm of circadian rhythmicity in epilepsy. The thalamus plays a critical role in generating sleep spindles and influencing seizure mechanisms, as discussed by Zarowsky and Loddenkemper[19-20]. They highlight thalamic modulation in neuronal synchronization and oscillations. Maybe it would suggest that DBS in the thalamus might offer innovative avenues for managing epilepsy. DBS shows potential to modify pathological brain rhythms, presenting a promising frontier for enhancing treatment strategies tailored to seizure chronobiology.

The MORE (Molecular Oscillations and Rhythmicity of Epilepsy) hypothesis, proposed by Bernard, posits that circadian rhythms and molecular oscillations significantly influence seizure timing and occurrence in epilepsy[25]. This theory suggests that biological processes regulated by 24-hour molecular oscillators, including gene and protein expression in the brain, play a pivotal role as summarized in Figure 1. Seizures often follow daily patterns, termed "seizure rush hours," indicating peak susceptibility during specific times. Understanding these molecular rhythms could lead to personalized treatments and chronotherapy approaches that optimize seizure management based on individual circadian profiles[25]. Chronotherapy, although promising, is currently underutilized due to the variability in seizure rhythms. Further exploration of chronotherapeutic approaches, such as sustained or pulsatile drug administration and the use of 'zeitgebers' to alter endogenous rhythms, could optimize seizure control in selected patients.

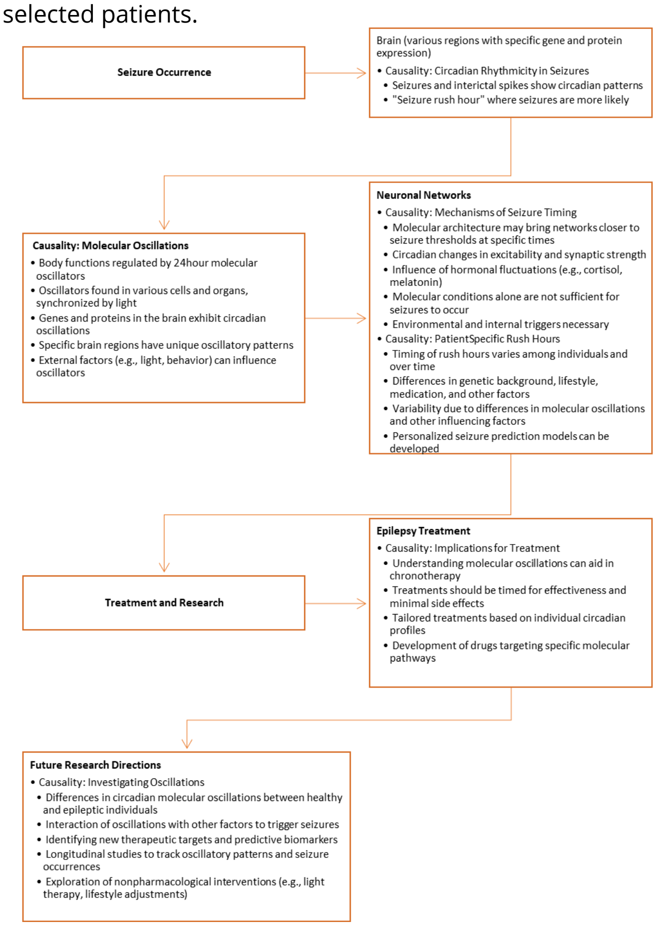

Figure 1. Understanding Circadian Influences on Epileptic Seizures based on the MORE (Molecular Oscillations and Rhythmicity of Epilepsy) hypothesis, proposed by Bernard[25].

CONCLUSION

Based on the reviewed studies on circadian rhythmicity in epilepsy, it is evident that temporal patterns play a significant role in the occurrence and typology of epileptic seizures. Most studies have revealed a strong influence of circadian rhythms and sleep-wake cycles on the characteristics of epileptic seizures, regardless of the seizure onset zone. Patients with TLE, for instance, exhibit a bimodal pattern of seizure distribution throughout the day, with specific peaks in the morning and afternoon.

These findings have significant implications for the clinical management of epilepsy. A better understanding of circadian patterns can aid in more accurate seizure prediction and personalized therapeutic strategies. The application of chronotherapy, which adjusts the administration of anti-seizure med according to periods of increased seizure susceptibility, emerges as a promising strategy to improve seizure control and minimize treatment-related side effects. Studies have shown that synchronizing patients' biological rhythms with treatment regimens can lead to significant improvements in quality of life and patient safety.

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