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Advancing Pediatric Epilepsy Care: Efficacy and Mechanisms of Melatonin Intervention

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Abstract

Seizures and epilepsies pose significant challenges in pediatric populations, necessitating precise classification and effective management. The International League Against Epilepsy updated its classification system in 2017 to standardize epilepsy care. This study investigated melatonin, a neurohormone known for its role in circadian rhythm regulation, and its potential to enhance the diagnosis, management, and quality of life of pediatric epilepsy patients. Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, a systematic review was conducted to explore the relationship between melatonin and pediatric epilepsies. PubMed searches were performed using specific search terms, with eligibility criteria including studies on melatonin's pathophysiological, biochemical, and therapeutic effects in pediatric epilepsy. Studies involving patients aged 0-18 years were published between 2003 and 2023. Four-teen studies with 898 pediatric patients were included. Melatonin was administered as an adjunct to antiepileptic therapy with the aim of alleviating disorders associated with epileptic encephalopathies or assisting electroencephalogram procedures. Findings were varied: Some studies indicated a reduction in seizure frequency with melatonin, while others provided inconclusive results. Improvements in sleep disorders related to epilepsy were noted with melatonin supplementation, which indirectly enhanced the overall quality of life. Melatonin has potential as an adjunctive therapy for pediatric epilepsy, with positive effects on seizure frequency and sleep quality. However, methodological limitations in some studies and inconclusive data underscore the need for further research to determine the efficacy of melatonin in pediatric epilepsy management. The diverse potential of melatonin in treating neurological disorders highlights the importance of continued, comprehensive research into its therapeutic application.

Keywords: Melatonin, melatonin receptors, pediatric epilepsy, seizure management, sleep disorders, antiepileptic therapy

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Introduction

Seizures and epilepsies are prevalent conditions in childhood, and accurate classification, management, and treatment are essential for effective patient care.[1] In 2017, the International League Against Epilepsy (ILAE) introduced a revised classification system for seizures, epilepsies, and epileptic syndromes. This update aimed to standardize epilepsy management and enhance communication among healthcare professionals for both scientific and diagnostic therapeutic purposes.[2] The updated ILAE classification system adopts a multilevel framework, including the categorization of seizure types[3], epilepsies, and, where applicable, the definition of epileptic syndromes.[4] Epilepsy, a debilitating disorder in pediatric patients, significantly impacts quality of life and requires prolonged treatment, often without complete seizure control and with potential comorbidities.[5,6] Given these challenges, pediatric epilepsy remains a dynamic and evolving field of research. There is a growing need to explore therapeutic agents that could improve the diagnosis, management, and quality of life of pediatric patients with epilepsy while also considering the risk of adverse effects associated with these treatments. Melatonin, a neurohormone produced by the pineal gland and locally in the retina, exhibits a circadian secretion pattern (elevated levels at night and reduced levels during the day).[7] Although melatonin is well known for its role in regulating circadian sleep-wake rhythms, cancer inhibition, free radical detoxification, and protection against oxidative stress, its potential antiepileptic properties have been less extensively studied.[8-10] Emerging scientific evidence suggests that melatonin may improve patients' quality of life by influencing sleep quality, reducing seizure frequency, and modulating oxidative stress.[11] This study aimed to evaluate the role of melatonin in enhancing the management of pediatric epilepsy and its potential benefits in improving overall patient outcomes.

Highlights

- **Epilepsy management::** The 2017 ILAE classification system aimed to standardize epilepsy care, particularly for children.
- **Role of melatonin:** Melatonin, which regulates circadian rhythms, may have potential in pediatric epilepsy treatment.
- **Systematic review:** A Preferred Reporting Items for Systematic Reviews and Meta-Analyses guided review of 14 studies (898 patients) examines melatonin's role in pediatric epilepsy.
- **Study findings:** Melatonin, an adjunct to antiepileptic therapy, may reduce seizures and improve sleep in children with epilepsy.
- **Variability in findings:** While some studies have shown positive effects of melatonin, others have been inconclusive, indicating a need for further research.
- **Quality of life:** Melatonin may indirectly improve quality of life by addressing epilepsy-related sleep difficulties.
- **Therapeutic potential:** Despite its limitations, melatonin demonstrates promise in pediatric epilepsy care, highlighting the need for extensive investigation.

Material and Method

Study Search Strategy

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (**Figure 1**). The search was independently conducted by two authors using PubMed. To ensure a comprehensive search, the following terms were combined: "Epilepsy" or "Epilepsy, Partial, Motor" or "Epilepsy, Partial, Sensory" or "Epilepsy, Benign Neonatal" or "Epilepsy, Reflex" or "Myoclonic Epilepsy, Juvenile" or "Epilepsy, Rolandic" or "Epilepsy, Frontal Lobe" or "Epilepsy, Complex Partial" or "Epilepsy, Post-Traumatic" or "Epilepsy, Temporal Lobe" or "Epilepsy, Absence" or "Epilepsy, Tonic-Clonic" or "Epilepsy, Generalized" or "Drug Resistant Epilepsy" or "Epilepsies, Myoclonic" or "Epilepsies, Partial" and "Melatonin" or "Receptor, Melatonin, MT2" or "Receptor, Melatonin, MT1" or "Receptors, Melatonin" as keywords or Medical Subject Headings terms. Additionally, the reference lists of all included articles and the top hits from PubMed were reviewed to identify further potentially relevant studies. To prevent overlap with ongoing reviews, international prospective register of systematic reviews was also searched for similar reviews.

Selection Criteria

Eligible studies included those investigating the pathophysiological, biochemical, and therapeutic actions of melatonin, its metabolic pathways, and its relation to pediatric epilepsies. We included articles examining melatonin's role in electroencephalogram (EEG) procedures, its potential interactions with anti-seizure drugs, and its impact on the overall quality of life of patients with epilepsy. Studies were excluded if they did not focus on pediatric patients (0 to 18 years), did not explicitly address the relationship between melatonin, its receptors, and epilepsy, or did not directly investigate aspects of EEG signal recording or quality in patients with epilepsy were excluded. Additionally, we excluded studies lacking accessible data or full text, articles in languages other than English, duplicates, and studies with inadequate scientific methodology. The search and evaluation were conducted independently by two authors (S.M.C. and D.B.), with any discrepancies resolved by F.F.C., an experienced researcher in systematic reviews. After applying the inclusion and exclusion criteria and reviewing the abstracts, the investigators reached a consensus. Only studies published between 2003 and 2023 that involved pediatric and adolescent patients (birth to 18 years) were included.

Data Extraction and Criteria Assessment

Data extracted included title, year of publication, study design, sample size, population characteristics, intervention, comparator (if applicable), outcomes, and conclusions. The data extraction followed the Population, Intervention, Comparison, Outcome

framework and was organized into structured tables using Excel. One investigator conducted the initial extraction, which was independently verified by another investigator. Two investigators, along with F.F.C., reviewed each article independently and resolved discrepancies through discussion and consensus. The final results were reviewed by the senior investigator (S.M.C.).

Risk of Bias Assessment

Risk of Bias (RoB) was assessed using the ROBINS-I tool for non-randomized studies and the RoB 2 tool for randomized trials. Two authors (F.F.C. and D.B.) performed the assessment independently, achieving a 92% inter-rater agreement. Discrepancies were resolved through discussion. Articles with serious RoB were excluded. The RoB assessment is detailed in tables 1aS and 1bS in the online resource.

Study Quality Assessment

The study quality was assessed using the GRADE approach. The initial grade was determined based on study design, with randomized trials providing high-quality evidence and observational studies providing low-quality evidence. Factors that could lower or increase quality were evaluated, resulting in an overall evidence grade (high, moderate, low, very low). Two authors (S.M.C. and F.C.) conducted this assessment independently, obtaining a 94% inter-rater agreement. Articles rated as very low quality were excluded. The quality assessment is presented in table 2S of the online resource.

Statistical Analysis

Descriptive statistics were used to summarize the characteristics of the study population, including demographics, intervention methods, and outcome measures. Quantitative outcomes, such as seizure frequency, sleep parameters, and EEG recordings, were analyzed using meta-analytic techniques when applicable. Random-effects models were used to account for heterogeneity among studies, with effect sizes and 95% confidence intervals estimated to assess the overall treatment effects of melatonin. Subgroup analyses were performed to explore variability based on factors such as age, epilepsy type, and melatonin dosage. Sensitivity analyses were conducted to evaluate the robustness of findings by excluding studies with high RoB or small sample sizes. Publication bias was assessed using funnel plots and Egger's test, with adjustments made if significant bias was detected. Statistical significance was defined as $p<0.05$.

Ethical Considerations

The research did not involve human or animal subjects, so ethical approval from the ethics committee was not required. All procedures adhere to standard ethical guidelines and academic research regulations. No consent form was required due to the study design.

Results

We identified 14 studies that examined the role of melatonin or its receptors in pediatric epilepsy (**Table 1**). The combined cohort of these studies included 898 patients who received melatonin as an adjunct to anti-seizure therapy. The primary aim of this study was to improve conditions associated with the underlying pathology in epileptic encephalopathies or to assist with EEG procedures.

Study Selection and Focus

Among the included studies, only two reviews by Kennaway[12] and Banerjee and Kumar[13] focused on the relationship between exogenous melatonin administration and its effectiveness as an anti-seizure therapy. These reviews also examined how melatonin affects the circadian rhythm of endogenous melatonin in patients with seizure, particularly addressing its role in pediatric patients with sleep-related epilepsy disorders.

Melatonin Levels and Epileptic Activity

Five studies investigated the correlation between melatonin levels and cerebral epileptic activity. These studies assessed variations in melatonin secretion among pediatric epileptic patients by analyzing both baseline secretion and levels during or shortly after seizures. A common finding was a reduction in basal melatonin levels or alterations in circadian rhythm among epileptic patients. Tarcin et al.[14] reported reduced basal melatonin levels in pediatric patients with status epilepticus and electrical status epilepticus during sleep (ESES) compared to controls. Similarly, Ayça et al.[15] observed lower serum melatonin levels at 9 a.m. in patients with ESES in a cohort of 39 pediatric patients.

Manni et al.[16] studied both adults and adolescents with juvenile myoclonic epilepsy using a semi-structured interview (Morningness-Eveningness Questionnaire), Pittsburgh Sleep Quality Index (PSQI), and salivary melatonin measurements. They found an altered circadian rhythm of melatonin levels in patients with epilepsy, potentially influenced by the epileptic condition.

The Pharmacological Therapeutic Role

Three studies explored melatonin's pharmacological role in treating typical childhood epilepsy. Sun et al.[17] and Wan et al.[18] examined melatonin's anticonvulsant activity in infantile spasms, either as an adjunct to or replacement for traditional anti-seizure therapy. Their studies indicated that melatonin, combined with adrenocorticotropic hormone (ACTH) or used alone significantly reduced spasm frequency and prolonged the period without spasms.

Verma et al.[19] conducted a randomized, double-blind, placebo-controlled clinical trial on the effect of melatonin in the treatment of generalized epilepsy with generalized-onset motor seizures in adolescents and adults. This study found that melatonin (3 mg/day) combined with valproate resulted in a significant reduction in seizure frequency, an increased seizure-free rate, and improved sleep quality.

Inconclusive Data

Some studies have provided inconclusive data regarding melatonin's efficacy in pediatric epileptic disorders. For instance, Brigo et al.[20] reviewed melatonin as an add-on therapy in 106 patients aged 18 years. Despite several promising results regarding seizure frequency reduction, the poor quality of some studies prevented definitive conclusions about melatonin's effectiveness as an add-on therapy.

Impact of Sleep Quality

Seven studies emphasized melatonin's effectiveness in improving sleep quality in children with epilepsy. Melatonin supplementation enhances the overall quality of life by improving sleep-related issues associated with epilepsy.

Bonuccelli et al.[21] conducted a double-blind, placebo-controlled study of 100 patients aged 1-6 years. They administered liposomal melatonin and performed sleep EEG. They found reduced sleep latency and improved EEG outcomes, thereby enhancing the efficiency of the procedure and the safety of melatonin use.

Gustafsson et al.[22] compared the EEG results of 129 children administered melatonin and 113 children subjected to sleep deprivation. Their study indicated that melatonin was more effective in inducing sleep in younger children (0-4 years) than in older children (9-12 years), likely due to greater sleep lability in younger patients. Jain et al.[23] observed that prolonged release of melatonin reduced sleep latency, increased rapid eye movement (REM) latency, and decreased REM sleep duration in pediatric patients (aged 6-11 years) over 4 weeks without worsening spike density or seizure frequency.

Additional Observations

Four studies noted improvements in sleep quality among pediatric patients with epilepsy and associated sleep disorders. Verma et al.[19] reported enhanced sleep quality, as measured by the PSQI, in patients with generalized epilepsy receiving melatonin together with anti-seizure medication. Myers et al.[24] conducted randomized controlled trials in patients with Dravet syndrome and revealed increased total sleep and improved quality of life with melatonin use.

Discussion

Melatonin is a hormone synthesized primarily by the pineal gland and is well known for its role in regulating circadian rhythms. In addition to its circadian functions, melatonin acts as a neuroregulatory hormone with notable immunoregulatory, anti-inflammatory, immunosuppressive, and antioxidant properties. These characteristics highlight the potential significance of addressing the pathophysiological mechanisms underlying neurological disorders, including epilepsy.

Extensive research has investigated melatonin's anticonvulsant properties through both *in vivo* and *in vitro* studies. For example, Mosìnska et al.[25] explored the anticonvulsant effects of melatonin receptor agonists in mice, whereas Solmaz et al.[26] demonstrated neuroprotective and anticonvulsant effects in male albino guinea pigs treated with high doses of melatonin (50-160 mg/kg), leading to reduced convulsion severity and mortality.

In the context of pediatric epilepsy, melatonin has shown promise as an adjunctive therapy to anti-seizure medications, positively influencing seizure frequency and overall quality of life. Verma et al.[19] conducted randomized, double-blind, placebo-controlled clinical trials and revealed favorable outcomes with a reduction in seizure frequency when melatonin was added to the treatment regimen for generalized epilepsy.

The potential therapeutic benefits of melatonin extend to infantile spasms. Wan et al.[18] demonstrated significant reductions in seizure latency and frequency in mouse models. Sun et al.[17] conducted a prospective, randomized, double-blind, placebo-controlled trial, confirming melatonin's efficacy and safety as an adjunct to ACTH therapy in patients with infantile spasm syndrome, particularly among those aged 3 months to 2 years.

Melatonin's utility in the pediatric population also includes its application in sleep EEG. Gustafsson et al.[22] compared EEG outcomes between pediatric patients receiving melatonin and those subjected to sleep deprivation. The study found that melatonin effectively addressed sleep difficulties without compromising the quality of brain electrical recordings. The interrelationship between sleep and epilepsy is complex, with many epilepsy types manifesting predominantly, if not exclusively, during sleep. For instance, interictal epileptiform activity is notably activated during N3 sleep, whereas seizures and interictal discharges are less frequent during REM sleep. This intricate relationship underscores the multifaceted impact of melatonin on both sleep and epilepsy.

Jain et al.[23] conducted a randomized, double-blind, placebo-controlled, crossover study involving children aged 6-11 years. Their study revealed a statistically significant reduction in sleep latency and improvements in overall quality of life and disease tolerance among patients with epilepsy.

Further support for melatonin's role in managing sleep disorders associated with epilepsy was reported by Kennaway et al.[12] and Banerjee and Kumar[13] Both studies independently confirmed melatonin's effectiveness in improving sleep disorders and highlighted its protective effects against convulsions. These findings collectively emphasize melatonin's potential as a multifaceted therapeutic agent for managing epilepsy and associated sleep disturbances.

Table 1. *Summary of results*

Authors and years of study	Sample age	The type of study	Epilepsy characteristics	Melatonin findings
Kennaway[12]		Review		Not possible to draw conclusions on the control of the frequency and severity of seizures regarding the use of melatonin as an add-on therapy in epileptic patients, or on the alteration of the circadian rhythm of melatonin, although it appears altered Improvement of sleep disorders in patients with epilepsy and sleep disorders
Banerjee and Kumar[13]		Review		Lower melatonin concentrations in children with seizures; effective in improving children's sleep by reducing the time; reduces the severity of seizures; and improves chronic sleep disorders in subjects with epilepsy
Tarcin et al.[14]	91 children with epileptic seizures	Case study	Generalized tonic-clonic epilepsy, absence epilepsy, juvenile myoclonic epilepsy, status epilepticus in sleep	Lower baseline melatonin levels in children with epileptic seizures and in the ESES group than in the control group
Ayça et al.[15]	39 children	Case control study	Continuous spikes and waves during sleep, and various epilepsy	Significant reduction in blood melatonin levels in patients with ESES
Manni et al.[16]	13 patients with juvenile myoclonic epilepsy	Case control study	Cryptogenic focal epilepsy juvenile myoclonic epilepsy	Onset of low-light melatonin occurs approximately 59 minutes later in generalized epilepsy, and the peak melatonin level in these patients was significantly lower than that of controls
Sun et al.[17]	70 patients aged 3-2 years	Randomized controlled trial	Infantile spasms	Short-term efficacy of melanin on infantile spasm
Wan et al.[18]	60 3-month-old, specific pathogen-free rats	Experimental preclinical study	Infantile spasms	Combined ACTH and melatonin treatment effectively reduced the number of spasms and increased latency in NMDA rats
Verma et al.[19]	104 patients aged 13-60 years. 21 were pediatric and adolescent patients	Randomized controlled trial	Generalized epilepsy with generalized onset motor seizures.	Add-on melatonin and valproate for generalized epilepsy with generalized-onset motor seizures can result in significantly better clinical outcomes Add-on melatonin improved the quality of sleep
Brigo et al.[20]	106 patients aged 18 years	Systematic reviews	Epileptic syndrome	Not possible to draw any conclusions regarding the role of melatonin in reducing seizure frequency or improving quality of life in people with epilepsy
Bonuccelli et al.[21]	100 children aged 1-6 years	Randomized controlled trial	Epileptic syndrome, febrile seizures, suspected seizures for sleep disturbance, behavioral problems/ psychomotor delay	Safety and efficacy of liposomal melatonin as a sleep inducer in pediatric patients with epileptic sleep
Gustafsson et al.[22]	232 patients, aged 1-16 years	Retrospective study	Generalized and focal epilepsy	Melatonin is equally efficient in inducing sleep and does not affect the occurrence of epileptiform discharges in EEG recordings
Jain et al.[23]	11 patients aged 6-11 years	Randomized controlled trial	Benign Rolandic epilepsy, childhood absence epilepsy, focal epilepsy	Statistically significant decreases in sleep Latency and wakefulness after sleep onset No clear effects on seizures
Myers et al.[24]	13 pediatric patients	Randomized controlled trial	Dravet syndrome	No increase in total sleep due to melatonin administration; clinical benefits on sleep disturbance
Yaşgüçlükal et al.[27]	59 children aged 4-15 years	Multicenter study	Epileptic encephalopathy with spike-and-wave activation in sleep	Lower melatonin levels in patients with EE-SWAS than in the control group

ESES; Electrical status epilepticus in sleep, ACTH; Adrenocorticotropic hormone, NMDA; N-methyl-D-aspartic acid, EEG; Electroencephalogram, EE; Epileptic encephalopathy, SWAS;Spike and wave activation in sleep

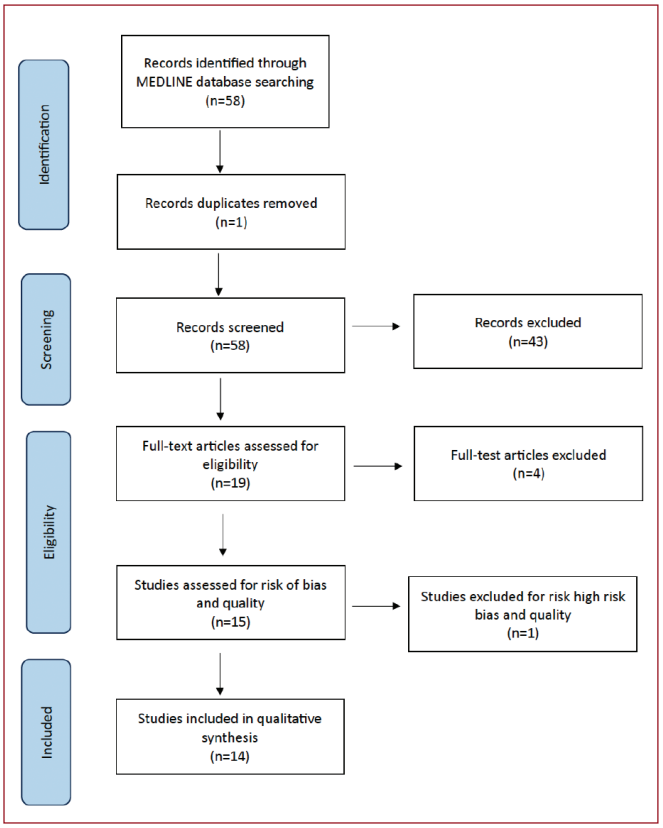

Figure 1. PRISMA flowchart of systematic search strategy. Data were added to the PRISMA template under the terms of the Creative Commons Attribution Licesence[28]

Conclusion

This review highlights the potential significance of exogenous melatonin in managing pediatric epileptic disorders. The findings suggest that melatonin may play a role in the pathophysiology of cerebral electrical disturbances, as indicated by fluctuations in blood melatonin levels during epileptic seizures. Notably, melatonin has shown promise in certain pediatric epilepsies, particularly when used as an adjunct to anti-seizure medications. Administration of this drug has demonstrated potential to reduce seizure frequency and improve overall treatment outcomes.

Additionally, melatonin is a safe and effective option for enhancing sleep quality during EEG procedures. By decreasing sleep latency, melatonin facilitates the optimal recording of cerebral electrical activity without compromising the accuracy of the EEG results. This benefit is particularly relevant for addressing sleep disorders that are frequently associated with pediatric epilepsy and epileptic encephalopathies.

Overall, the integration of exogenous melatonin into therapeutic strategies for pediatric epilepsy has promise as a multifaceted intervention. The potential to improve sleep quality and reduce seizure frequency underscores its value in enhancing the overall quality of life of pediatric patients. Further research is needed to fully elucidate its efficacy and establish standardized guidelines for its clinical use.

Informed Consent: The consent form was not needed due to the study design.

Author Contributions: Salvatore Michele Carnazzo: Surgical and Medical Practies, Concept, Design, Literature Search, Writing.; Desirèe Balconara: Data Collection or Processing, Literature Search, Writing.; Francesco Fabrizio Comisi: Concept, Analysis or Interpretation.; Martino Ruggieri: Analysis or Interpretation.

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