



# The Need for Antiepileptic Drug Chronotherapy to Treat Selected Childhood Epilepsy Syndromes and Avert the Harmful Consequences of Drug Resistance

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**ABSTRACT:** Antiepileptic drug (AED) chronotherapy involves the delivery of a greater AED dose at the time of greatest seizure susceptibility usually associated with predictable seizure peaks. Although research has proven AED chronotherapy, commonly known as differential dosing, to be safe, well tolerated, and highly effective in managing cyclic seizure patterns in selected childhood epilepsies, conventional, equally divided AED dosing remains the standard of care. Differential dosing is more often applied in the emergency management of acute seizure clustering resulting from drug resistance—a harmful epilepsy-related consequence that affects 30% of children. Moreover, drug resistance is a major risk factor in status epilepticus and sudden, unexpected death in epilepsy. Although these facts should promote the wider use of differential dosing in selected cases, a credible hypothesis is needed that defines the differential dosing strategy and application in cyclic epilepsy and for the greater purpose of preventing harmful outcomes.

**KEYWORDS:** AED chronotherapy, differential dosing, conventional dosing, drug resistance, status epilepticus, sudden, unexpected death in epilepsy, chronotherapeutic mechanism

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## Introduction

Chronotherapy is a medically established symptom-based treatment strategy of unequally dosing commonly prescribed medications or therapies to enhance therapeutic action on “target tissues” in chronic disease.<sup>1</sup> In epilepsy, antiepileptic drug (AED) chronotherapy, commonly known as differential dosing, requires a larger AED dose at the time of day or night when circadian-modulated biorhythms linked to seizure exacerbation are predicted to peak.

Differential dosing is an emerging means to safely optimize AED efficacy for improved seizure control particularly in selected childhood epilepsies that follow circadian patterns of seizure exacerbation and remission.<sup>2,3</sup> There is evidence that differential dosing can extend seizure control and delay or prevent drug resistance—a major risk factor in both status epilepticus (SE) and sudden, unexpected death in epilepsy (SUDEP).<sup>3,4</sup> Despite the credible research demonstrating the utility of differential dosing, medical practitioners have been slow to accept it as the preferred intervention in pediatric seizure management. Conventional or equally divided AED dosing is commonly prescribed to treat all epilepsy types. Differential dosing is mainly used to treat acute seizure emergencies often resulting from drug resistance secondary to failed conventional AED dosing.<sup>4</sup>

## Drug Resistance in Epilepsy

Chronic epilepsy affects nearly 500 000 children in the United States, and 30% will become drug resistant—a serious epilepsy-related complication and a significant public health

burden—related to inadequate or failed seizure control from 2 or more conventionally dosed AEDs.<sup>5–10</sup> Drug resistance presents more than an epilepsy management challenge; it is among the leading risk factors for SE and SUDEP.<sup>11–14</sup> The danger of drug resistance and other SUDEP risk factors is often inadequately addressed in the literature.<sup>11</sup> Research has shown that practitioners avoid discussing SUDEP with patients with epilepsy, families, or caregivers.<sup>15</sup>

The hallmark of drug-resistant epilepsy is seizure clustering defined as a period of repetitive seizures with short interseizure intervals that fail to naturally terminate after 5 minutes.<sup>16</sup> Seizure clustering can lead to SE, a life-threatening encephalopathy that requires rescue drugs to break and intensive care hospitalization.<sup>17</sup> In the United States, the annual incidence of SE related and unrelated to drug resistance is approximately 20 to 30 cases per 100 000, and children are twice as likely as adults to experience at least 1 episode of SE by the time they reach adulthood.<sup>18,19</sup>

Severe drug resistance is a major risk factor for SUDEP. Aptly described, SUDEP is the sudden, unexpected death of persons with epilepsy that occurs with or without witnesses, with or without postmortem evidence of seizure, and without a physical, traumatic, or toxicologic cause.<sup>11,13</sup> Devinsky reported that among epileptic adults with one or more SUDEP risk factors, the incidence of SUDEP per 1000 patient-years is 6.0 to 9.3. The annual mortality rates of SUDEP in infants and children are considered unreliable but are suspected to be at least comparable to adults.<sup>11</sup> Actual SUDEP cases in infancy are



believed to be underrecognized and underreported especially because unexplained death in infancy is often attributed to sudden infant death syndrome.<sup>20</sup>

The potential danger of drug-resistant epilepsy should motivate medical practitioners to initiate differential dosing early in the epilepsy diagnosis in selected cases not only to improve and prolong seizure control but also to reduce the risk of harmful or fatal outcomes.

### Harmful Outcomes in Epilepsy

Current epilepsy research has proven the safety and efficacy of differential dosing for children with chronic, circadian-driven cyclic epilepsy syndromes.<sup>3,4</sup> Another benefit of differential dosing is longer seizure control which can delay or prevent drug resistance and reduce the risk of SE and SUDEP. The application of differential dosing for SUDEP prevention was recommended by Devinsky<sup>11</sup> who boldly proposed increasing the nighttime AED dose in adults and children with nocturnal tonic-clonic (TC) epilepsy as TC epilepsy is a known risk factor for SUDEP at any age.

The reluctance among many medical practitioners to implement differential dosing to treat cyclic seizures<sup>21</sup> or to mitigate harmful outcomes could be alleviated with a credible hypothesis of how AED chronotherapy works in epilepsy. This could motivate the medical community to use differential dosing for purposes of extending seizure control and to delay or prevent drug resistance and avert harmful outcomes.

### Chronotherapy Use in Chronic Disease

The study and practice of chronotherapy in treating chronic disease are not new. Pharmacologic chronotherapy has a proven track record most notably in asthma, diabetes, and cancer treatment. Burioka and colleagues<sup>22</sup> described how chronotherapy can control life-threatening nocturnal asthma attacks and improve drug tolerance in adults with moderate-to-severe asthma. The authors reported that patients who had a nighttime dose of the bronchodilating agent theophylline during their circadian-modulated patient-specific phase of peak expiratory flow rate (PEFR) helped them predict and treat the early morning phase of low-level lung function more accurately and improve respiratory symptoms.<sup>22</sup> Although the circadian phase of lowered lung function is necessary for pulmonary homeostasis, reduced lung function in asthma disease can lead to severe asthma attacks.<sup>23</sup>

Chronotherapy in type 2 diabetes involves the application of long-acting and short-acting insulin preparations combined to cover predictable fluctuations in diurnal, circadian, and meal-based blood glucose levels. This strategy was specifically designed to target and prevent the harmful symptoms related to exogenous and endogenous circadian-modulated glucose peaks in patients with type 2 diabetes.<sup>24</sup>

Evidence linking improved outcomes in patients with advanced peripheral organ cancers with late afternoon chemotherapy treatments helped cancer researchers discover the optimal time to deliver cytotoxins and maximize cancer cell

damage.<sup>25</sup> The drug cisplatin is known to kill cancer cells by forming bulky lesions on DNA.<sup>26</sup> Gaddameedhi and colleagues discovered that the circadian-modulated DNA nucleotide excision repair (NER) pathway removes bulky DNA lesions induced by UV light and is highly active in the morning and less active in the afternoon.<sup>27-29</sup> Patients who received cisplatin chronochemotherapy in the afternoon during the endogenous phase of low NER pathway activity benefited from optimum cancer cell destruction and improved outcomes. Another advantage of chronochemotherapy is that patients reported less of the debilitating side effects suffered by patients on variably timed chemotherapy regimens.<sup>26-29</sup> Despite these benefits, chronochemotherapy has yet to be accepted as a significant therapeutic parameter in chemotherapy protocols.<sup>30</sup>

Certain childhood epilepsies like other chronic illnesses are influenced by circadian rhythms. Children with chronic cyclic epilepsy can be safely managed with AED chronotherapy and benefit from reduced drug toxicity and improved alertness. Despite the proven advantages of differential dosing to date its use is limited.<sup>3,4,31,32</sup> The main reason why medical practitioners are reluctant to use differential dosing to treat epilepsy<sup>21</sup> or chronochemotherapy to treat cancer<sup>30</sup> is likely because a credible hypothesis of the underlying chronotherapeutic mechanism has yet to be formalized. Unfortunately, this fact has likely impeded the advancement of chronotherapy use in chronic disease across many fields of medicine.

### Suprachiasmatic Nucleus and Central Clock: The Circadian Link to Epilepsy

The molecular mechanism(s) involved in circadian seizure frequency variations in humans is not well understood, but some mechanistic insight is available from animal models. The research by Ralph and colleagues<sup>33</sup> established the suprachiasmatic nucleus as the site of the central biologic clock or circadian pacemaker in mammals. The authors determined that the central pacemaker, commonly known as the circadian system, is a robust, dynamic equilibrating scheme responsible for driving gene expression in central and peripheral circadian oscillators necessary for metabolic equilibrium and homeostatic stability throughout the body.<sup>33</sup> Damiola and colleagues<sup>34</sup> provided further evidence to support the existence of endogenous central and peripheral circadian oscillators in mammals that modulate biorhythms of energy homeostasis in 24-hour cycles.

The circadian involvement in mammalian epilepsy was demonstrated by Quigg and colleagues<sup>35</sup> in rodents with mechanically induced mesial temporal lobe epilepsy (MTLE). The authors observed seizures occurred every 24 hours during the light cycle or sleep phase in nocturnal animals.<sup>35</sup> In later research, Quigg<sup>36</sup> reported that human subjects with MTLE had increased seizures in the early evening as the circadian-initiated sleep phase approached.

These discoveries suggest that seizures in MTLE are activated close to or during the habitual sleep state in nocturnal and diurnal species secondary to a pathologic epileptic process

that disrupts the normal circadian-driven sleep state no matter when sleep occurs.

### Circadian Regulation of Non-REM Sleep and Influence in Epilepsy

The complex phenomenon of sleep is highly conserved across species and is orchestrated by 2 mutually exclusive but interactive mechanisms—the circadian oscillatory system and the homeostatic regulator—that together consolidate the sleep process.<sup>37,38</sup> The circadian system's role in sleep ontogeny is to initiate early non-rapid eye movement (NREM) sleep stages N1 and N2 and rapid eye movement (REM) cycles. The initiation of REM sleep and the start and conservation of deep sleep or N3, commonly referred to as slow wave sleep (SWS), are believed to be under homeostatic control.<sup>38</sup>

Pavlova and colleagues<sup>39</sup> shed some light on the circadian system's role in normal sleep ontogeny and adverse involvement in sleep-potentiating epilepsy. This research assessed the continuous day/night electroencephalographic (EEG) data of 5 adult subjects with well-controlled TC epilepsy and quantified the wake/sleep variations of interictal epileptiform discharges (IEDs). Interictal epileptiform discharges are benign EEG seizure patterns that do not evolve into electroclinical seizure events. Final results showed a predominance of IEDs in sleep compared with waking by a ratio of 14:1 ( $P < .001$ ) and almost exclusively during the circadian-driven NREM sleep stages N1 and N2.<sup>39</sup> Significantly, IEDs were found to be suppressed during waking and during established REM sleep cycles,<sup>39</sup> which is the physiologic element of sleep believed to be maintained by homeostatic regulators.<sup>38</sup>

These findings provide evidence supporting the circadian regulation of IEDs in adults with active, well-controlled TC epilepsy because IEDs were more prevalent in N1 and N2 sleep. The fact that IEDs were greatly reduced in the homeostatic-regulated REM cycles and when present failed to organize into electroclinical seizures further supports the circadian system's regulation of early sleep and the intimate, adverse relationship between early sleep cycles and seizure activation in TC epilepsy.<sup>37–40</sup>

Stanley and colleagues examined data of complex networks of genes expressed in rodent brainstem nuclei and basal ganglia to illustrate the complexity of circadian gene regulation in what they referred to as a “bidirectional relationship” between diurnal rhythms and cyclic epilepsy. The authors suggested that epileptic seizures disturb endogenous circadian cycles of gene regulation in the central nervous system (CNS).<sup>41</sup> Mirzoev and colleagues<sup>31</sup> described the cyclic nature of seizures in various focal epilepsy types that are passively activated by the circadian rhythm of a gene or genes expressed in specific brain regions in 24-hour cycles.

Mirzoev et al more accurately described the relationship between endogenous circadian cycles and focal epilepsy patterns and provided insight as to why differential dosing works. The chronotherapy strategy when applied to epilepsy can improve

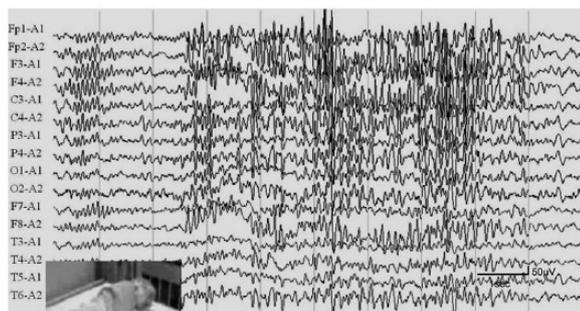
and prolong drug efficacy and pharmacokinetic action when a greater AED dose is timed with the circadian period of peak seizure occurrence. Conversely, conventional dosing in circadian epilepsy can adversely affect AED pharmacokinetic properties by impeding absorption, metabolism, and excretion and lead to poor seizure control, drug toxicity, and drug resistance.<sup>9</sup>

### Homeostatic Regulation and Relative Seizure Freedom of Slow Wave Sleep

Homeostatic-regulated SWS is believed to be a dynamic, restorative physiologic period necessary for the maintenance of peak metabolic and endocrine functions necessary for life.<sup>42,43</sup> Slow wave sleep in humans is also theorized to be a critical neurophysiologic period essential for memory consolidation and higher intellectual functions, including complex learning.<sup>44,45</sup> The SWS pattern seen on EEG could possibly emulate a phase of lowered neocortical activity required for brain homeostasis in the same way that PEFR predicts when the phase of lowered lung function, necessary for normal pulmonary homeostasis, will occur.<sup>23</sup>

The theory that SWS is critical for memory and learning<sup>44,45</sup> while at the same time crucial for maintaining innate functions and the equilibria of multiple organ systems<sup>42,43</sup> suggests that SWS is vital for CNS homeostasis. The SWS pattern seen on EEG could possibly emulate a phase of lowered neocortical activity required for brain homeostasis in the same way that PEFR identifies when the phase of lowered lung function, necessary for normal pulmonary homeostasis, will occur.<sup>23</sup> As in asthma, when the phase of homeostatic-lowered lung function can lead to asthma attacks, the complex processes of brain homeostasis could require reduced neurophysiologic activity and result in neocortical excitability that in person predisposed to epilepsy can cause adverse symptoms.<sup>2</sup> The onset of SWS could signal the endogenous phase of CNS homeostasis that in epilepsy can destabilize the neocortex before sleep transitions to lighter, circadian-driven NREM stages. This could be the scenario for seizure activation in autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE). Seizure clusters begin approximately 2 hours after habitual sleep onset, at the end of the first SWS cycle, and early in the transition to N2 sleep.<sup>31,46</sup> Seizure activation in N2 lends credence to the theory of neocortical destabilization<sup>3</sup> and excitability<sup>2</sup> during the homeostatic-regulated SWS stage that precedes the circadian transition to N2 sleep. The nocturnal seizure pattern of ADNFLE in children and adults is very similar when time is adjusted for differences in sleep onset or bedtime. Seizure clusters peak between 01:00 and 03:00 in children and 05:00 and 07:00 in adults, at the same point of sleep ontogeny after SWS transitions to N2.<sup>3,31,46</sup> These findings substantiate not only the inertness of SWS to activate, organize, or maintain electroclinical epileptic seizures but also its capacity to predispose the brain to seizure activation during early NREM stages.

The adverse association between early NREM sleep and seizures is a significant fact often understated in epilepsy research.



**Figure 1.** Electroencephalographic seizure sample of a preteen with autosomal dominant nocturnal frontal lobe epilepsy. The first of 3 seizures in a cluster began after midnight. The focal seizures originated in the right frontal lobe (Fp2 lead). At seizure onset, the child lay motionless with eyes open for 3 to 4 seconds and then began thrashing the limbs vigorously, fist punching, nonsensical verbalization, and screaming. Referenced from Tomonoh et al.<sup>52</sup>

Loddenkemper and colleagues acknowledged an intimate relationship between early NREM sleep and seizure activation based on EEG findings. The authors considered this only an assumption because the EEG data analyzed in their research were not recorded using the standard polysomnographic monitoring equipment used to stage sleep.<sup>3</sup> But according to the work of Rechtschaffen and Kales,<sup>47</sup> sleep stages can be accurately identified using EEG data alone.

### Evidence of Seizure Activation in Circadian N2 Sleep

Mirzoev and colleagues reviewed the literature of multiple EEG studies that investigated focal epilepsy in adults. They concluded that focal seizure cycles are predictable in both waking and sleep but peak at different times depending on the epileptogenic zone that generates them.<sup>31</sup> The authors speculated that although the area of brain onset dictates seizure semiology, the circadian cycle(s) specific to that brain region governed timing<sup>31</sup> and used the seizure peak timing differences between frontal lobe and temporal lobes as examples. They observed that in **frontal lobe disease**, seizures peaked during NREM sleep more than 50% of the time. In contrast, temporal lobe seizures tended to peak in waking during the late afternoon, an observation Quigg et al<sup>35</sup> reported in humans with MTLE. Mirzoev et al noted that in ADNFLE, nocturnal seizures clustered consistently in N2 and speculated that 24-hour circadian phases activated generalized seizures in the same way. The authors referred to N2 as “spindle sleep” due to the characteristic sine waves on EEG, as the sleep stage most susceptible to seizure activation due to an anomalous yet to be identified interrelationship with epilepsy.<sup>31</sup>

Regarding reports of exogenous melatonin treatment and nocturnal seizure exacerbation in adult epilepsy, Mirzoev et al<sup>31</sup> supported a causal relationship. The authors were likely influenced by reports of an aberrant association between increased endogenous melatonin levels and seizure activation.<sup>9,48</sup> The work by Pavlova and colleagues<sup>39</sup> vindicated endogenous melatonin as the cause of increased seizures. Pavlova et al noted that

endogenous melatonin normally increases in N2 sleep possibly to promote, maintain, and advance habitual sleep. This makes the rise in melatonin a robust biomarker and the one sleep physiologists depend on to detect N2 sleep onset.<sup>39,49</sup> The natural rise of melatonin in N2 sleep and the epileptogenicity of N2 sleep are associated but are distinct neurophysiologic phenomena. This might explain why many epilepsy researchers believe that high amounts of melatonin can cause seizures.

### Utility of Differential Dosing in Focal and Generalized Cyclic Epilepsy

The focal seizures of ADNFLE follow a cyclic pattern of seizure exacerbation in sleep and remission in waking. Cyclic seizure patterns are also common in generalized epilepsy.

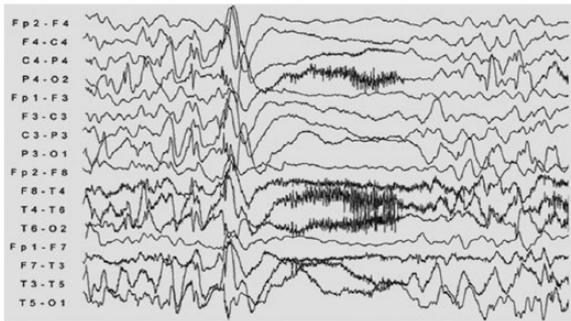
X-linked infantile spasm syndrome 1 (ISSX1) is a form of epileptic infantile spasm seizures that is not formally recognized by the International League Against Epilepsy (ILAE) as a generalized or sleep-activated epilepsy.<sup>7</sup> Because the electroclinical seizures that characterize ISSX1 are considered **cyclic, follow** a strict circadian pattern of exacerbation and remission, and are followed by habitual sleep this important seizure type will be considered a sleep-potentiated generalized epilepsy type going forward.

Both ADNFLE and ISSX1 exhibit distinctive, cyclic, or circadian-driven electroclinical seizures<sup>2,3</sup> activated in the early stages of circadian NREM sleep. Figure 1 shows a seizure in ADNFLE. The sleep-potentiated focal seizures tend to cluster approximately 2 hours after sleep onset and occur almost exclusively during N2 sleep.<sup>31,46</sup> Figure 2 shows a seizure onset in ISSX1. The epileptic infantile spasms that characterize ISSX1 began to cluster at the transition period between circadian-modulated N1 sleep, or drowsiness,<sup>38</sup> and morning awakening and when waking from naps.<sup>7,50,51</sup> Although epileptic infantile spasm seizures resolve spontaneously after infancy, they commonly evolve into other complex focal and generalized seizure types that persist throughout life<sup>50,51</sup> and often present many risk factors linked to SE and SUDEP, including severe drug resistance.

The differential dosing of a larger AED amount at bedtime in children with ADNFLE assures that the therapeutic drug level and mode of action reach peak performance during the circadian phase linked with predicated seizure risk.<sup>2,4</sup> The lower AED dose commonly results in the natural fall of serum concentrations to nontherapeutic levels when seizure risk is low and leads to improved cognition, drug tolerance, and fewer side effects.<sup>4</sup> The nontherapeutic AED levels during seizure remission might even provide the neocortex a respite from pharmacologic intervention which could improve overall brain function and prepare the brain to receive treatment more efficiently when seizure risk is high.<sup>3,4</sup>

### Epilepsy Research on the Application of AED Chronotherapy in Children

AED chronotherapy research in adult and pediatric populations has provided evidence in support of differential dosing as



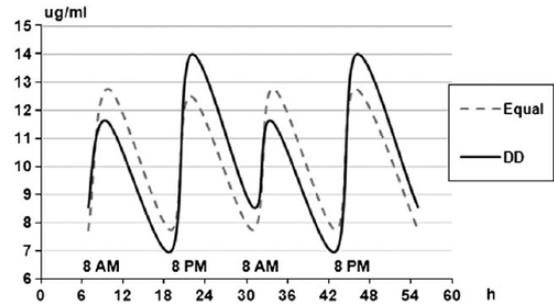
**Figure 2.** Electroencephalographic (EEG) seizure sample of an infant with X-linked infantile spasm syndrome 1. Epileptic spasm seizures began on awakening and continued over several minutes. Abnormal EEG activity preceded repetitive episodes of high amplitude, polymorphic spike, and slow wave complexes or “bursts” clinically associated with body flexion. Low amplitude or “suppressed” faster rhythms were associated with tonic stiffening of the limbs. Referenced from Panayiotopoulos<sup>53</sup> (Chapter 7, Figure 7.1).

a safe and effective method of controlling epilepsy, maintaining therapeutic drug concentrations, and reducing drug toxicity and side effects.<sup>3,4,31,32</sup>

For children with chronic epilepsy syndromes, Guilhoto and colleagues<sup>4</sup> proved that differential dosing was particularly efficacious in reducing or suppressing focal and generalized epilepsy types that exhibited predictably timed seizure clusters presumed to be associated with endogenous circadian rhythms. Guilhoto et al analyzed the medical records of 17 children between 3.5 and 21 years of age with various chronic seizure types, including ADNFLE, hospitalized for acute seizure clustering, and treated with differential AED dosing. The authors assessed the safety and efficacy of differential dosing in comparison with the conventional dosing schedules all of the children were formerly prescribed. Seizure diagnoses were based on the findings of long-term audiovisual EEG data collected over several consecutive days and according to ILAE seizure classification.<sup>7</sup> Individual cases were followed and reevaluated after a 12-month period.<sup>4</sup>

Guilhoto et al provided strong evidence to support the safety and efficacy of differential dosing particularly in the treatment of cyclic seizures in children. In cases of TC epilepsy, the larger nighttime AED dose resulted in improved seizure control. Figure 3 illustrates how the larger nighttime dose of carbamazepine leads to peak therapeutic levels at the time of peak seizure risk. This finding could indicate the brain's greater susceptibility to targeted treatment at night<sup>54</sup> and/or **more efficient pharmacokinetic action** of carbamazepine during habitual sleep.<sup>9</sup> The lower daytime AED dose resulted in lowered therapeutic drug levels during the school day and benefited children with improved energy and alertness.<sup>3</sup>

Guilhoto et al proved that differential dosing resulted in faster, improved outcomes in children with focal and generalized nocturnal epilepsies compared with the control group of



**Figure 3.** Equal and differential antiepileptic drug (AED) dosing in nocturnal epilepsy. Equal (ED) and differential (DD) dosing of the AED carbamazepine used to treat nocturnal tonic-clonic epilepsy. The daytime peaks of serum drug levels associated with DD are lower than in ED. Nighttime levels are higher with DD when seizures are known to peak. Referenced from Guilhoto et al.<sup>4</sup>

children treated with conventional dosing. Children tolerated differential dosing better than conventional dosing and showed less toxicity and fewer side effects. The final results were impressive and revealed that differential dosing lead to seizure freedom in 64.7% of children and seizures reduced by half in 88.2% of children.<sup>4</sup>

Guilhoto et al supported the circadian involvement in seizure activation. They reported that a close relationship exists between day/night circadian patterns and seizures in epilepsy and suggested that the normal alternations of excitatory and inhibitory thalamocortical circuits involved in the circadian regulation of NREM sleep could behave pathologically and stimulate seizures in the epileptic brain.<sup>4</sup>

Loddenkemper and colleagues<sup>3</sup> presented a comprehensive case study analysis of 1008 seizures in 225 children diagnosed with various focal and generalized epilepsy types. The authors found that the state of consciousness, waking or sleep, was a more accurate marker of seizure type and origin of onset than the time of day when seizures occurred. This reinforced the circadian system's control of sleep and the influence of circadian phases on seizure exacerbation in and out of sleep.

Regarding epilepsy diagnosis and treatment, Loddenkemper and colleagues<sup>2</sup> expounded on the dynamic interaction between sleep and epilepsy and the genetic regulation of epilepsy by the circadian system during sleep. The authors provided a clearer understanding of the circadian process and role in seizure activation and the success of AED chronotherapy in controlling circadian-dependent seizures. The authors supported the utility of differential dosing in selected circadian-regulated epilepsy syndromes and suggested that the improved efficacy of AED chronotherapy is a way to provide patient-oriented treatment in cases of circadian-dependent seizures.<sup>2</sup> Loddenkemper et al legitimated the term chronoepileptology in reference to differential dosing and the use of “zeitgebers” such as light therapy to help realign shifted circadian phases suspected in specific cases of increased seizure activation.<sup>2,41</sup>

Zarowski and colleagues<sup>32</sup> provided evidence gathered from the retrospective analysis of a large cohort of children hospitalized for the management of chronic, predictable, sleep-related generalized epilepsy. In this study, seizure diagnoses were deemed highly reliable and based on ILAE classification standards<sup>7</sup> and results from consecutive days of audiovisual EEG monitoring, seizure tracking logs prepared by parents and caregivers, and close adherence to AED dosing schedules. The authors reported that sleep-potentiated generalized seizures were activated either from established sleep or when arising from sleep. They stressed the importance of distinguishing between evening and morning seizure preponderance and suggested that the circadian system regulates certain generalized epilepsies.<sup>32</sup> Zarowski et al<sup>32</sup> also reported seizure predictability based on the fact that generalized cyclic seizures in children were more common in sleep and that epileptic infantile spasm clusters showed 2 peaks both associated with the transition of sleep to waking in the morning and from the afternoon nap.

Although the expert research analyzed in this review substantiates the safety and efficacy of differential dosing in controlling certain childhood epilepsy syndromes, the more common application of differential dosing is in response to acute seizure clustering secondary to drug resistance—often the outcome of inadequate AED choice or dosage.<sup>3,4,9,32,55</sup> The most common approach to managing drug-resistant epilepsy and the one recommended by the ILAE is AED substitution—a strategy that in itself presents new risks.<sup>7,8,56</sup> AED manipulations in the setting of increased seizures augment the likelihood of drug toxicity and other adverse side effects.<sup>4</sup> Multiple AED use or polytherapy is another serious risk factor linked to SUDEP.<sup>11,14</sup>

The fact remains that as new AEDs are trialed often over several months and medication adjustments are made to offset new side effects, children continue to suffer with debilitating seizures that lead to marked cognitive impairment, overall delayed development, and steady reduction in the quality of life. Cho reported that epilepsy specialists are often unwilling to prescribe differential AED dosing in new cases of epilepsy mainly because there is no viable hypothesis of the chronotherapeutic mechanism.<sup>21</sup> The use of differential dosing in the acute management of seizure clustering further perpetuates the notion that differential dosing is an emergency treatment and not a method to extend seizure control. The main reason for the limited use of the differential AED dosing method is likely because differential dosing contradicts ILAE's expectation of equally divided AED dosing as the standard of care.

### Research Results of Differential Dosing in Adults Extrapolated to Children

Mirzoev and colleagues<sup>31</sup> reported positive findings of differential AED dosing in adults, including improved seizure control, reduced AED toxicity, and maintenance of therapeutic drug levels. The authors also suggested a lowered seizure threshold in the epileptic brain predominantly during N2 sleep

secondary to aberrant signals that travel along the same thalamic pathways known to generate the sleep spindles that characterize N2 sleep.<sup>31</sup> This observation has been corroborated by others in epilepsy research.<sup>2,4,40,41</sup> Mirzoev et al<sup>31</sup> noted similarities between adult and childhood focal epilepsy types, including the consistent timing of day/night seizure peaks and stereotypical seizure patterns. These features of focal epilepsy depend on the area of seizure onset in the brain.

Yegnanarayan et al<sup>54</sup> performed one of the earliest and largest clinical trials of differential AED dosing efficacy. A cohort of 148 adult subjects diagnosed with and under treatment for generalized, sleep-potentiated epilepsy were followed for 12 months. Subjects were categorized according to their daily AED dosing amounts. The study subjects were differentially dosed and received 25% of the total daily AED dose in the morning and 75% in the evening or the entire dose in the evening. The control subjects were conventionally dosed and received equally divided doses twice daily. Both groups were closely monitored for AED compliance by caring family members.<sup>54</sup>

At the end of 1 year, the authors reported that the study group experienced faster seizure control and an improved overall response, including lowered seizure frequency and reduced adverse effects, and had achieved adequate drug maintenance levels. None of the control subjects experienced any positive results.<sup>54</sup>

According to an earlier adult study led by Yegnanarayan,<sup>54</sup> the evening dose of the AED phenytoin when compared with the morning dose showed a better pharmacokinetic effect, including faster and more efficient absorption and reduced toxicity and side effects. The improved response could have been due to better drug pharmacokinetic action in the evening hours related to habitual sleep.<sup>4</sup> Similarly, in asthma, the nighttime prophylactic dose of theophylline improved lung function by morning in time for the endogenous circadian phase of reduced pulmonary function when the risk of asthma attacks was known to peak.<sup>22,23</sup>

Although most of the clinical trials and retrospective case studies of AED chronotherapy have been carried out in adult subjects,<sup>31,54</sup> the benefits of differential dosing, including improved seizure control, reduced incidences of drug toxicity, and maintenance of therapeutic levels, can be extrapolated to children affected by the same epilepsy disorders.<sup>31</sup> Other common features between adult and childhood epilepsy include the circadian influence of seizure exacerbation, the propensity for drug resistance, the risk of SE, and the fatal outcome of SUDEP.

### Methods

- Four retrospective case study investigations of AED chronotherapy use in up to 225 children ranging from 3 months to 20 years with various pediatric seizure types and AED treatment schedules were evaluated.

**Table 1.** Case studies investigating antiepileptic drug chronotherapy.

Circadian patterns of pediatric seizures, Loddenkemper et al. <sup>3</sup>
Circadian profiles of focal epileptic seizures: A need for reappraisal, Mirzoev et al. <sup>31</sup>
Circadian distribution and sleep/wake patterns of generalized seizures in children, Zarowski et al. <sup>32</sup>
Higher evening antiepileptic drug dose for nocturnal and early morning seizures, Guilhoto et al. <sup>4</sup>

Children were hospitalized for acute seizure clustering secondary to drug resistance while on conventional AED dosing.

- Seizure diagnoses were made according to ILAE seizure classification, and AEDs were prescribed according to ILAE treatment guidelines.
- The chronotherapy method was assessed in subjects who received a greater amount of the total daily AED dose based on the predictable circadian patterns of day/night seizure peaks. The lower amount was given during the predicted period of seizure remission.
- With the exception of the review by Mirzoev et al,<sup>31</sup> seizure diagnoses were based on results from at least 1 day and up to 10 consecutive days of audiovisual EEG monitoring during extended hospitalizations in tertiary epilepsy centers. Parents or caregivers prepared detailed written seizure logs to track seizure frequency and report new seizure types. All patient-seizure information, AED, and dosing schedule were documented in electronic medical records during hospitalization.
- Six general requirements were applied to each case study to test the claim that AED chronotherapy when compared with conventional AED dosing can provide faster seizure control with fewer side effects in cases of acute seizure clustering.

Table 1 lists the 4 retrospective case studies analyzed in this review. All case studies observed and documented seizure exacerbation and remission patterns in subjects with chronic epilepsy. Each case study assessed the utility and safety and efficacy of differential AED dosing. Three of the case studies evaluated the potential use of differential AED dosing to treat focal and/or generalized epileptic seizures,<sup>3,31,32</sup> and 1 study was treatment based<sup>4</sup> and examined actual differential AED dosing results in children with either focal or generalized epilepsy.

Tables 2 to 5 highlight the 6 general requirements applied to each case study, including the type of epilepsy under investigation, reliability of epilepsy diagnosis, observation of seizure pattern, use of differential AED dosing, evidence of improved seizure outcome, and whether drug resistance was identified by the authors as a risk factor with potential harmful consequences.

**Table 2.** Requirements to test the hypothesis applied to circadian patterns of pediatric seizures.

REQUIREMENT	REQUIREMENT MET
Seizure type(s) identified	Yes (focal and generalized)
Reliable epilepsy diagnoses	Yes (based on ILAE seizure classification, LTM, electronic medical records, and seizure tracking logs)
Differential AED dosing schedules used	N/A
Patterns of seizure exacerbation and remission observed	Yes
Evidence of improved seizure outcomes and reduced side effects secondary to differential AED treatment	N/A
Associated drug resistance with harmful consequences	No

Abbreviations: AED, antiepileptic drug; ILAE, International League Against Epilepsy; LTM, long-term monitoring.

**Table 3.** Requirements to test the hypothesis applied to circadian profiles of focal epileptic seizures: a need for reappraisal.

REQUIREMENT	REQUIREMENT MET
Seizure type(s) identified	Yes (focal)
Reliable epilepsy diagnoses	Sometimes (some focal seizure types were classified according to ILAE classification and nonvideo EEG findings)
Differential AED dosing schedules used	N/A, although discussed
Patterns of seizure exacerbation and remission observed	Yes
Evidence of improved seizure outcomes and reduced side effects secondary to differential AED treatment	N/A
Associated drug resistance with harmful consequences	No

Abbreviations: AED, antiepileptic drug; EEG, electroencephalographic; ILAE, International League Against Epilepsy.

## Results

Tables 6 to 9 include condensed synopses of each case study's objective, methods, results, and final conclusions along with the authors' retrospective interpretation of the original data. Individual case study findings of focal and generalized epilepsy are listed.

Loddenkemper et al<sup>3</sup> reported that the waking or sleep states are more reliable than daytime or nighttime hours at predicting seizure activation and confirming seizure types (Table 6).

**Table 4.** Requirements to test the hypothesis applied to circadian distribution and sleep/wake patterns of generalized seizures in children.

REQUIREMENT	REQUIREMENT MET
Seizure type(s) identified	Yes (generalized)
Reliable epilepsy diagnoses	Yes (based on ILAE seizure classification, LTM, electronic medical records, and seizure tracking logs)
Differential AED dosing schedules used	N/A
Observed patterns of seizure exacerbation and remission	Yes
Evidence of improved seizure outcomes and reduced side effects secondary to differential AED treatment	N/A
Associated drug resistance with harmful consequences	No

Abbreviations: AED, antiepileptic drug; ILAE, International League Against Epilepsy; LTM, long-term monitoring.

**Table 5.** Requirements to test the hypothesis applied to higher evening antiepileptic drug dose for nocturnal and early morning seizures.

REQUIREMENT	REQUIREMENT MET
Seizure type(s) identified	Yes (focal and generalized)
Reliable epilepsy diagnoses	Yes (based on ILAE seizure classification, LTM, electronic medical records, and seizure tracking logs)
Differential AED dosing schedules used	Yes (differential AED dosing was compared with conventional AED dosing schedules in treating focal and generalized epilepsy types)
Observed patterns of seizure exacerbation and remission	Yes
Evidence of improved seizure outcomes and reduced side effects secondary to differential AED treatment	Yes (positive correlation made between differential AED dosing and focal and generalized seizure control with seizures that follow predictable patterns of exacerbation and remission)
Associated drug resistance with harmful consequences	No

Abbreviations: AED, antiepileptic drug; ILAE, International League Against Epilepsy; LTM, long-term monitoring.

In focal epilepsy, the brain's origin of seizure onset can influence local circadian rhythms which can lead to seizure peaks.

Mirzoev et al<sup>31</sup> reported that AED treatment in focal epilepsy has been negatively affected by the fact that the circadian influence in focal epilepsy is underappreciated. Predictable seizure patterns and mechanisms of activation in adult focal epilepsy types are similar in childhood forms. A credible

hypothesis of the aberrant mechanism(s) that connects normal circadian rhythms with epileptic events is sorely needed and will require a collaboration of several sciences to accomplish (Table 7).

Zarowski et al<sup>32</sup> reported that the predictable timing differences in seizure clustering among various focal and generalized childhood epilepsies are secondary to separate, distinct circadian rhythms that regulate seizure activation to predominate in either the waking or sleep state (Table 8).

The treatment-based research by Guilhoto et al<sup>4</sup> found that children with predictable focal nighttime and generalized daytime 24-hour seizure cycles who developed drug resistance and acute seizure clustering while on conventional dosing schedules regained seizure control quickly and with few side effects secondary to the differential dosing of 75% of the total AED amount at night (Table 9).

Common findings among all 4 case studies are listed:

- All case studies supported the circadian oscillatory system's involvement in seizure propagation in cyclic epilepsy based on the predictability of seizure exacerbation and remission and promoted this observation as the most significant factor to support the need for AED chronotherapy.
- Seizure clusters that occurred during habitual nighttime sleep were considered sleep potentiated. Seizure clusters that occurred on morning awakening were considered daytime events.
- All case studies supported the classification of epileptic infantile spasm seizures as nongeneralized waking events.
- All case studies missed the opportunity to emphasize the need for AED chronotherapy by acknowledging the success of differential AED dosing not only as a safe and effective method of controlling acute seizure clustering but also as a means to improve and extend seizure control and expressly to avert or prevent drug resistance, a known epilepsy-related consequence that affects 30% of children with epilepsy and is a major risk factor in both SE and SUDEP.

## Discussion

Each retrospective case study analyzed in this review agrees that differential AED dosing is safe and effective in cyclic seizure management. None addressed the need for differential AED dosing to prolong seizure control or prevent drug resistance. This was very concerning because drug resistance is a known epilepsy-related consequence that affects 30% of children treated with conventional AED dosing and a major risk factor in SE and SUDEP.<sup>13,56</sup>

The reluctance among researchers to acknowledge the need for AED chronotherapy to treat selected epilepsy types or to delay or prevent drug resistance is most likely because the ILAE holds an impartial position on differential AED dosing.

**Table 6.** Case study objective and synopses of methods, results, and conclusions.

METHODS	RESULTS	CONCLUSIONS
Two-year retrospective case study review of 1008 primary seizures in 225 children aged 2.5 to 14 years hospitalized for the acute increase in focal or generalized seizures determined to be resistant to conventional AED dosing	Waking and sleep are more reliable for predicting seizures, accurate seizure classification, and AED management particularly for epilepsy syndromes influenced by circadian rhythms. Nocturnal focal seizures occurred more often in sleep (00:00-06:00), and generalized seizures occurred more often on awakening (06:00-12:00)	The “epileptogenic zone” or brain origin of seizure onset likely influences cyclic seizure peaks of circadian rhythm(s) that predominate during a period of cortical susceptibility to seizure activation. Waking or sleep can predict seizure origin of onset, semiology, and the incidence of clustering secondary to circadian influences over sleep and epilepsy

Abbreviations: AED, antiepileptic drug.

Loddenkemper et al assessed whether waking and sleep were more reliable markers than day and night in predicting focal and generalized pediatric seizure patterns.

**Table 7.** Case study objective and synopses of methods, results, and conclusions.

METHODS	RESULTS	CONCLUSIONS
Retrospective analyses of the current epilepsy research that reported on the peak timing differences among various focal seizures in adults (and children) as a function of the brain’s origin of cortical onset	Circadian periodicity of focal epileptic seizures exists in adults, and differences in seizure timing are based on the origin of cortical seizure onset. Adult focal seizure patterns are very similar in children. Seizure clustering in adult cases of ADNFLE peak between 05:00 and 07:00 and between 01:00 and 03:00 in children (due to an earlier bedtime)	The circadian influence of focal epilepsies is underappreciated. This fact impacts AED treatment. The collaboration of epileptology and chronobiology could lead to the discovery of the aberrant mechanism(s) involved in circadian seizure exacerbation and novel treatments and improve focal and generalized epilepsy management

Abbreviations: ADNFLE, autosomal dominant nocturnal frontal lobe epilepsy; AED, antiepileptic drug.

Mirzoev et al reviewed multiple case studies to determine whether circadian phases (acting on the brain’s origin of seizure onset) are responsible for the timing differences known to occur among various types of focal epileptic seizures.

**Table 8.** Case study objective and synopses of methods, results, and conclusions.

METHODS	RESULTS	CONCLUSIONS
Five-year retrospective study of 316 seizures in 77 children aged 3 months to 20 years hospitalized for drug-resistant focal or generalized (TC) epilepsy. Seizure clusters occurring between 06:00 and 18:00 were classified as daytime. Seizure clusters that occurred between 18:00 and 06:00 were classified as nocturnal	Different types of generalized seizures cluster at different times more than 24 hours because they are driven by separate, endogenous circadian rhythms. Most TC seizures cluster at night between 18:00 and 06:00. Infantile spasms (central to ISSX1) cluster in waking in the early morning 06:00-09:00 and again around 15:00 but could be associated with drowsiness (N1)	Pediatric-generalized epileptic seizure exhibits an awake or sleep predominance according to type. This distinction and accurate seizure diagnosis can help guide individualized treatment, including differential AED dosing schedules and other treatment options

Abbreviations: AED, antiepileptic drug; ISSX1, X-linked infantile spasm syndrome 1; TC, tonic-clonic.

Zarowski et al assessed the timing of seizure clusters associated with various types of TC epilepsy relative to distinct circadian phases active in the sleep or waking states.

**Table 9.** Case study objective and synopses of methods, results, and conclusions.

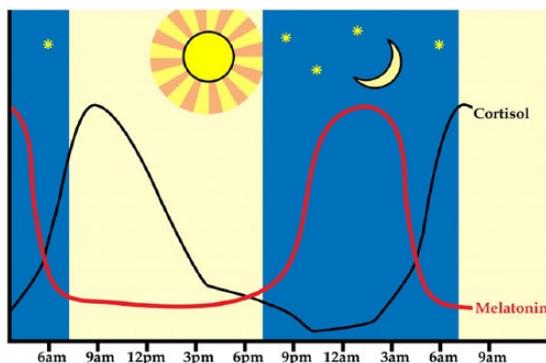
METHODS	RESULTS	CONCLUSIONS
One-year retrospective case study of 17 children aged 3.5 to 20 years hospitalized for drug-resistant nocturnal focal or generalized (TC) early morning epileptic seizures treated with differential AED dosing with ¾ of the total daily dose taken at night	Differential AED dosing resulted in seizure freedom in 64.7% of cases and in reduced seizure frequency in 88.2%	Differential AED dosing ¾ of the total daily dose at night proved to be safe and more effective than conventional equally divided AED dosing by providing better seizure control in drug-resistant pediatric epilepsies associated with predictable circadian seizure patterns

Abbreviations: AED, antiepileptic drug; TC, tonic-clonic.

Guilhoto et al assessed the efficacy of differential AED dosing in the acute seizure management of children with focal and generalized drug-resistant epilepsy on conventional AED dosing.

The ILAE neither supports nor opposes the application of differential AED dosing under any circumstance. But the ILAE appears to presume that AEDs are prescribed according

to conventional dosing standards.<sup>7</sup> In this regard, nonconventional AED dosing challenges the standard of care expected by ILAE although this is only an assumption.



**Figure 4.** The circadian-driven hormones cortisol and melatonin occur out of phase. Cortisol peaks during the waking hours and melatonin peaks during habitual sleep (<http://www.thepaleomom.com/2014/02/regulating-circadian-rhythm.html>).

### Limitations of the Case Studies

The research by Guilhoto and colleagues examined the efficacy of differential dosing to regain seizure control in focal epilepsy, including ADNFLE and generalized nocturnal TC seizures. Although results of differential dosing in cases of epileptic infantile spasms were reported, subjects diagnosed with infantile spasms or subjects who had an early diagnosis of epileptic infantile spasms that had naturally evolved into other seizure types after infancy were not included. The omission of this important generalized seizure type with all the earmarks of circadian-driven epilepsy and the one very well suited for differential dosing left the treatment of epileptic infantile spasms unchallenged. One possible reason is that epileptic infantile seizure spasms are not classified as focal or generalized seizures nor are they considered sleep potentiated by most of the investigators (or by the ILAE) even though the seizure clusters that characterize epileptic infantile spasms are generalized and closely follow habitual sleep and are activated as sleep transitions to the waking state in the morning and after naps.<sup>50,51</sup>

Guilhoto et al speculated on the possible relationship between CNS seizure mechanisms and patterns of circadian-modulated seizures and considered pharmacokinetic differences among AEDs specifically regarding absorption and elimination rates and peak levels but did not ponder how the chronotherapeutic mechanism enhanced AED action with respect to the circadian timing of seizures.<sup>4</sup> In support of the circadian involvement in seizure activation, the authors reported that a close relationship exists between day/night circadian patterns and seizures in epilepsy. They also suggested that the normal alternations of excitatory and inhibitory thalamocortical circuits involved in the circadian regulation of NREM sleep could behave pathologically and stimulate certain seizure types in the epileptic brain.<sup>4</sup> Although the authors supported the circadian regulation of NREM sleep and pathologic influence of epilepsy in circadian NREM sleep, they did not comment whether or not N2 sleep was more susceptible to seizure activation.

Although their results were promising, Guilhoto et al remained skeptical and concluded that differential AED dosing alone could not explain such impressive results.<sup>4</sup> This was mainly due to the fact that the greater AED dose at night led to improved seizure control with only minor drug level peaks.<sup>4</sup> This finding could have prompted them to consider that minimal AED peaks reflected improved pharmacokinetic activity provided by the higher nighttime dose. Ramgopal and colleagues<sup>9</sup> indirectly suggested this possibility when reporting that the endogenous central and peripheral circadian oscillators necessary for regulating brain functions and metabolic activity in distant organ systems could positively or negatively affect AED pharmacokinetic efficacy.

Loddenkemper and colleagues reported that the complex circadian-driven sleep processes that produce robust sleep spindles—the characteristic feature of N2 sleep—follow the same inhibitory and excitatory thalamocortical oscillatory pathways theorized to generate seizures in epilepsy.<sup>3,40,46</sup> The work by Loddenkemper et al<sup>3</sup> was poised to expand on the strict circadian influence of epilepsy in early sleep with data highlighting seizure activation in N1 and N2, but did not speculate further because the EEG data analyzed in their research were not recorded according to the polysomnographic monitoring standards currently used for proper sleep staging. The authors were correct in identifying N2 as the circadian sleep stage of seizure activation in ADNFLE in children and adults<sup>3</sup> and could have implicated early sleep in seizure activation based on EEG data alone by applying the sleep stage scoring guidelines perfected by Rechtschaffen and Kales.<sup>47</sup> Loddenkemper et al<sup>3</sup> also reported that epileptic infantile spasms tend to occur more commonly in the waking state, but a close examination of the authors findings indicated that infantile spasms are more likely sleep stage dependent because seizure clusters are known to begin at the transition from early NREM sleep in the N1 or drowsy period that precedes morning awakening and awakening from naps.<sup>32,50,51</sup> In this way, epileptic infantile spasms are more of a sleep-potentiated type of epilepsy.

Zarowski and colleagues determined that many generalized seizures occur during sleep, and the epileptic seizure clusters in infantile spasm occur during the transitional period from N1 sleep to waking in 2 peaks—on morning awakening and waking from naps.<sup>3,32</sup> The close association with N1 sleep and seizure clustering in infantile spasms as suggested is actually a sleep-potentiated generalized seizure type prone to circadian seizure activation. Along the same line, Zarowski et al also implied that the decreased cortisol levels found in infants diagnosed with epileptic infantile spasms were abnormal and possibly diagnostic of the disorder. It is known that cortisol and melatonin are circadian-driven hormones that naturally occur out of phase with each other across the 24-hour day (Figure 4). In fact, cortisol reaches trough levels in the late evening as melatonin levels peak. The inverse relationship between cortisol and melatonin speaks not only to the strong circadian drive to

promote sleep and regulate endocrine functions<sup>4,32,39,43</sup> but also to the possibility that the sleep process is integral to the activation of generalized seizures including epileptic infantile spasms.

Regarding hormone regulation, Loddenkemper et al<sup>3</sup> identified a connection between the abnormal modulation of hormones and seizure activation and suspected that, in certain epilepsies, circadian modulators of endocrine activity, and the neurohormone melatonin, are abnormally offset during the daytime and nighttime hours and can influence the waking and sleep seizure patterns associated with various focal and generalized epilepsies. The authors also speculated on the future of epilepsy management, including therapeutic treatments designed to reset circadian endocrine cycles in the waking and sleep states as a way to inhibit focal seizure activation at specific brain locations.<sup>3</sup> This observation could have been expanded to explain how differential AED dosing can help this process along with improving seizure outcomes.

The most significant inadequacy common to all the case studies was the fact that none warned against the dangerous connection drug resistance has with SE and SUDEP.

### Chronotherapy Use in Chronic Diseases Including Epilepsy

Chronotherapy involves timing medical treatment(s) to align with the endogenous circadian rhythms involved in normal metabolic processes that in chronic disease states can “trigger” adverse symptoms. In asthma, the chronotherapeutic nighttime application of the bronchodilating agent theophylline is timed to coincide with the natural circadian phase of lowered pulmonary function—a state of normal lung homeostasis—that in asthma sufferers can lead to life-threatening asthma attacks.<sup>22,23</sup> In type 2 diabetes, the application of chronotherapeutic insulin preparations can help minimize the adverse effects of normal day/night fluctuations of glucose peaks.<sup>24</sup> In cancer treatment, cisplatin chronochemotherapy administered during a normally low circadian phase of NER activity can destroy more cancer cells and result in improved outcomes and reduced side effects.<sup>27–29</sup>

Guilhoto et al<sup>4</sup> reported that AED chronotherapy can preempt focal and generalized seizures that follow predictable circadian cycles of exacerbation and remission. The EEG seizure clusters associated with epileptic infantile spasms and ADNFLE have been observed to begin in circadian-driven N1 and N2 sleep stages, respectively.<sup>46,50,51</sup> Mirzoev et al<sup>31</sup> speculated on the existence of an aberrant connection between the neuropathology of epilepsy and the N2 (spindle) sleep stage. Zarowski et al<sup>32</sup> reported on the involvement of inhibitory and excitatory thalamic circuits in the normal generation and synchronization of sleep spindles in NREM sleep, specifically N2, as well as the activation of seizures along the same pathways in epilepsy. Researchers agree that sleep involves complex interactions among various physiologic (circadian) oscillatory systems and networks that communicate with

thalamic structures known to generate sleep spindles in N2 sleep.<sup>3,4</sup> Curiously, none of the authors addressed why N2 sleep is especially seizure prone. This observation could have strengthened the circadian influence of seizures in ADNFLE and support the use of AED chronotherapy in selected cases.

Regarding the circadian influence of nocturnal seizures, the research by Loddenkemper and colleagues<sup>3</sup> reported that sleep potentiated seizures but did not qualify the stage(s) of sleep where seizures most commonly occurred as part of their investigation. Loddenkemper et al stated that the reason for this was that the standard sleep monitoring parameters used to distinguish NREM stages and REM were not applied to the EEGs in the database. However, sleep staging or sleep stage scoring can be determined using EEG brain wave activity alone according to the EEG sleep scoring guidelines prepared by Rechtschaffen and Kales.<sup>47</sup> The confirmation of N1 and N2 sleep in seizure activation could have strengthened and supported the differential AED dosing argument by linking the circadian control of early sleep with the circadian influence in epilepsy.

With the exception of Zarowski et al, most authors agreed that the epileptic infantile seizure spasms characteristic of ISSX1 are activated in the waking state. In a brief reference to established sleep staging criteria, Zarowski et al<sup>32</sup> alluded to the possibility that epileptic infantile spasm seizures could be more closely related to drowsiness (the circadian-driven sleep stage N1) than to the waking state. This observation was accurate if one considers the EEG criterion described by Rechtschaffen and Kales<sup>47</sup> and corroborated by Dijk and colleagues<sup>37,38</sup> years later that distinguished N1 as the earliest stage of NREM sleep. In the field of EEG, N1 is also referred to as drowsiness and is characterized by the loss of posterior waking brain rhythms (alpha waves) and the appearance of continuous, low-amplitude slower rhythms (theta waves) and the absence of sleep spindles.<sup>37,38</sup> The versatility of N1 distinguishes it as a transitional stage that can advance to N2, precede REM, and transition the sleep state into the waking state. In this regard, a closer examination of the morning seizure clusters of ISSX1 from a sleep physiology perspective would likely have convinced most authors that epileptic infantile spasm seizure clusters are not waking seizures at all but are in fact under circadian influence because they are activated in the sleep transitional stage N1. The fact that seizure activation does not occur from the homeostatic sleep-regulated stages of SWS or established REM further supports the circadian involvement and activation of seizures and defends differential AED dosing as a logical treatment strategy in selected cases.

More research is needed to determine why normal endogenous circadian rhythms behave abnormally in the setting of epilepsy and how differential AED dosing improves seizure outcomes safely, and with fewer side effects than conventional dosing, in cases of drug-resistant seizure clustering. The chronotherapeutic response in epilepsy is in line with the beneficial

results provided by the chronotherapeutic strategies in managing other cyclic, chronic illnesses, such as asthma and diabetes mellitus, and in cancer treatment based on the cyclic phases of cellular vulnerability. A credible hypothesis of the chronotherapeutic mechanism(s) in relation to pharmacokinetic properties of AEDs could reveal the success of differential dosing and the success of AED chronotherapy in seizure control. Improved AED pharmacokinetic designs and seizure prediction and detection technologies<sup>57,58</sup> could also improve the lives of children living with epilepsy.

In most of the case studies, seizure diagnoses were based on the results gathered from consecutive days of prolonged EEG monitoring in tertiary medical centers and seizure events logged and documented in electronic medical records. Seizure classifications and AED choices were made according to ILAE guidelines.<sup>7</sup>

In all case studies, authors either failed to report SE histories in their subjects or control for subjects with SE histories which likely confounded statistical analyses and final results because children with the history of SE who are commonly affected by more severe epilepsy types might not have responded to differential AED dosing in the same way as children without a history of SE.

### The Standard of Care: What Is Acceptable Medicine?

The success of AED chronotherapy in childhood epilepsy is based on the circadian influence of seizures that follow 24-hour circadian patterns of exacerbation and remission. But the standard of care set by the ILAE's latest classification of epilepsy syndromes and seizure types does not acknowledge a causal relationship between circadian rhythms and epilepsy in focal or generalized type of seizures. The ILAE does not imply the use of differential AED dosing in cases of drug resistance.<sup>7</sup> Although the ILAE formed a special task force for the express reason of defining drug-resistant epilepsy to medical practitioners to improve seizure outcomes in patients and to benefit epilepsy research, the ILAE referred to drug resistance relative to seizure "clustering" as a "pharmacoresistant occurrence to be expected along the natural course of certain epilepsy syndromes"<sup>57</sup>

Regarding AED treatment regimes, it appears that the ILAE assumes the use of conventional, equally divided dosing as the standard of care and neither acknowledges nor refutes differential AED dosing practices.<sup>7,8</sup> In recent ILAE publications regarding the topic of drug resistance in epilepsy, differential AED dosing is not discussed not even as an alternative to failed conventional dosing regimens in acute seizure clustering or as a means to avert harmful epilepsy-related consequences in patients with one or more SUDEP risk factors.<sup>7,8,57</sup> In fact, the ILAE's recommendation for the treatment for "pharmacoresistance" is switching to a new AED as a monotherapy or in combination with other AEDs (polytherapy) at clinically effective dosages with the expectation that conventional dosing schedules will be applied. From that point,

seizure freedom was reported to require at least 12 months. The ILAE's recommendation of AED substitution in drug-resistant epilepsy is not without risks.

The ILAE describes epilepsy as a dynamic but tenuous neurophysiologic process prone to ebb and flow along a natural course which can include pharmacoresistance.<sup>7</sup> Epilepsy in remission can temporarily relapse in the setting of common stressors such as febrile illness or worsen more permanently over time and become refractory to the AED(s) that once provided good control.<sup>7,8,57</sup> It appears that the ILAE proceeds with caution regarding differential dosing particularly in new or evolving epilepsy. This is likely because drug toxicity and side effects in conventional dosing can be severe and warrant immediate AED discontinuation.<sup>8,9,57</sup> For these reasons, it would be safer to prescribe conventional, equally divided AED dosing from the onset even to treat cyclic seizures to manage drug toxicity in the event of refractory epilepsy. These are legitimate concerns implied by the ILAE based on the recommendation of AED substitution and the expectation that conventional dosing schedules will be prescribed.

The way to create confidence in the application of AED chronotherapy is with a credible hypothesis that describes the circadian mechanism(s) in seizure exacerbation. An improved understanding of how AED chronotherapy works could lead to its wider use in acute drug-resistant epilepsy as well as in the primary management of cyclic seizures. This would require the collaboration of scientists across a broad range of medical disciplines, including epileptology, chronobiology, and sleep physiology, to discover the chronotherapeutic mechanism and how AED chronotherapy works. An improved understanding of AED chronotherapy could lead to the research and development of novel treatments, including smart drugs designed with improved pharmacokinetics capable of interacting with and disrupting the epileptic process and reducing the seizure burden in children.

### Author Contributions

Sheryl Manganaro reviewed four articles that reported the chronotherapeutic treatment of circadian epilepsy. Data was analyzed and the conclusion made supporting AED chronotherapy. The manuscript was drafted by Sheryl Manganaro under the guidance of co-authors Alexander Rotenberg, M.D., Ph. D. and Tobias Loddenkemper, M.D. Sheryl Manganaro, Alexander Rotenberg, and Tobias Loddenkemper approved the final version of the manuscript.

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