1. Introduction

Sleep is a universal human need, and suboptimal sleep has a detrimental impact on individuals and the society. The short-term health consequences of insufficient sleep range from augmented stress reactivity and somatic pain, to mood disorders and cognitive performance deficits [1,2]. Over the long term, mortality from all causes is elevated with sub-optimal sleep, and specific health impacts include hypertension, dyslipidemia, obesity, and cardiovascular disease [1,3,4]. An estimated 13% of workplace injuries have been attributed to poor sleep [5], and sleep-related performance failures have been linked to environmental disasters from nuclear meltdowns to oil spills [6].

Sleep disorders compound many existing problems faced by people with epilepsy; they can worsen or trigger seizures, and they can in turn be exacerbated by seizures and by anti-seizure treatments [7]. Sleep is, therefore, an important aspect of patient care that should not be overlooked, and one where we have the potential to improve patients’ overall health and quality of life. Still, it is an aspect that is rarely discussed. As one parent of a child with sleep-related seizures put it, “No one has ever discussed with us how this [epilepsy] affects his sleep and our sleep. No one has asked about our sleeping arrangement” [8].

To guide clinicians on this important topic, a group of experts from three scientific societies have recently published recommendations for identifying and managing poor night-time sleep and daytime sleepiness in people with epilepsy. We recommend that a comprehensive clinical history of sleep habits and sleep hygiene be obtained from all people with epilepsy and their bed partners. A psychoeducational approach to inform patients about habits or practices that may negatively influence their sleep or their vigilance levels should be used, and strategies for avoiding these should be applied. In case of a suspected comorbid sleep disorder an appropriate diagnostic investigation should be performed. Moreover, the possible presence of sleep fragmentation induced by sleep-related seizures should be ruled out. Finally, the dose and timing of antiepileptic medications and other co-medications should be optimized to improve nocturnal sleep and avoid daytime sedation.

© 2021 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).
dations to standardize the diagnostic pathway for sleep-related epilepsies and comorbid sleep disorders [7]. These experts suggested guidance for the management of sleep disorders in this population. However, there is a lack of Class I and Class II studies, and further work is necessary to produce sound evidence-based guidelines for managing common sleep disorders in people with epilepsy. These need to take into account the impact of anti-seizure medications (ASMs) on nocturnal sleep and daytime vigilance levels.

In recognition of this need, Kataria & Vaughan [9] in 2016 suggested several algorithms for managing excessive sleepiness and insomnia in people with epilepsy. However, only a limited guidance was provided on how to optimize ASMs in people with epilepsy and sleep problems.

In this article, we provide practical recommendations for neurologists and epileptologists for identifying and, in particular, for managing sleep disorders in people with epilepsy. Our recommendations build on the recent diagnostic approach for sleep-related epilepsies and comorbid sleep disorders [7], and expand on this to cover every-day problems of insufficient sleep or excessive sleepiness experienced by people with epilepsy.

1.1. The mechanics and functions of sleep

To date, the nature and functions of sleep remain poorly understood [10,11], but it is generally considered to be an active process with a unique fingerprint of neuronal circuitry inhibitions and activations, and with associated physiological consequences throughout the entire body [12–15].

1.1.1. Sleep structure

Distinct stages of sleep are characterized by marked changes in brain functional organization, with a major contrast being between rapid eye movement (REM) and non-REM (NREM) sleep [16]. Sleep onset starts with a short period of NREM sleep (stage N1) that progresses through stage N2, N3, and leads to REM sleep [11,16]. NREM sleep constitutes about 75–80% of total time spent in sleep, while REM sleep forms the remaining 20–25% [17]. The functional relationship between the two types of sleep remains a matter of ongoing debate [11,16]. During NREM sleep, the EEG is dominated by lower frequencies, in the delta (0–4 Hz) and theta (4–7 Hz) ranges, and prolonged periods of wake are followed by increased NREM sleep with high delta activity [18].

REM sleep portion increases as the night progresses, and it is characterized by low-amplitude, mixed-frequency EEG waves, skeletal muscle atonia due to brainstem-mediated inhibition of alpha motor neurons, and burst-like saccadic eye movements and peripheral muscle twitches [16].

1.1.2. Sleep function

Traditionally, it has been argued that interictal discharges and their propagation may increase during NREM sleep, in turn unmasking the epileptic network otherwise hidden during wakefulness [17]. Interictal epileptiform discharges during sleep can be associated with different NREM constituents (e.g. slow waves, sleep spindles), which are known to play a role in memory and learning [17]; Indeed, NREM slow waves play a role both in homeostatic sleep regulation and in brain plasticity (memory and learning) [19]. The original synaptic homeostasis hypothesis of Tononi and Cirelli argues that the exponential decline of sleep slow-wave activity parallels the downscaling of synapses potentiated by the cognitive activity performed in pre-sleep wakefulness (for in-depth review, see [19]). In addition to this function of NREM sleep, synaptic potentiation (upscaling) and memory consolidation may similarly occur within the hippocampo–frontal brain circuitry during slow-wave sleep [17]. The coupling and fine-tuning of the three major NREM oscillations (slow waves, spindles, and sharp-wave ripples) likely renders the cortex receptive to plastic changes [20]. More specifically, it has been suggested that spatio-temporal patterns of neuronal activity during encoding in the awake state become re-activated during NREM slow wave sleep (N3) [20]. Such replays promote the gradual redistribution of hippocampus-dependent memories from the hippocampus to neocortical sites for long-term storage (system consolidation) and might also trigger enduring synaptic changes to stabilize memories (synaptic consolidation). For an in-depth review see [20].

It is assumed that most dream mentation occurs during REM sleep, although dreams can occur during other sleep stages. REM sleep is considered critical for brain maturation, and its role is increasingly recognized in various neural and cognitive activities.

These range from basic mechanisms to complex processes, such as procedural and declarative learning, emotional memory processing, and the maintenance and development of consciousness [16].

1.1.3. Sleep circuitry

Wake- and sleep-promoting mechanisms are summarized in Table 1. Note that fast neurotransmitters like glutamate and GABA are now considered central to sleep–wake regulatory systems, with monoaminergic and cholinergic arousal systems serving a modulatory role [12,21].

1.1.4. Importance of sleep

The importance of sleep is highlighted by its preservation through species and through consequences of sleep deprivation, which, depending on the severity and an individual vulnerability, may span from mild-to-severe cognitive and neuropsychiatric deficits, homeostatic imbalance, immune dysfunction, and death [2,3,22–24].

An estimated 35% of American adults get less than the recommended 7–9 h of sleep; 69% of adolescents get less than the recommended 8–10 h [25,26]; and problems falling asleep or daytime sleepiness affect up to 40% of the population [27]. Despite the huge scale of the problem, the full economic and health impact is unknown. The cost of sleep disorders in Europe was estimated at €35.4 billion in 2010 [28], and performance failures caused by sleep loss and shift-work have been linked to nuclear reactor meltdowns at Three Mile Island and Chernobyl, as well as the grounding of the Star Princess cruise ship and the Exxon Valdez oil tanker [6].

Particularly relevant for people with epilepsy are, in addition to the potential risk of exacerabtng seizures, the significant neurocognitive deficits [29], psychosocial issues, mental health problems, and reduced overall quality of life [1] that result from inadequate sleep – areas that are already significantly impacted by epilepsy itself and its treatment.

1.2. Sleep and epilepsy

1.2.1. Sleep disorders and disturbances in people with epilepsy

Sleep disorders are approximately twice as common in people with epilepsy compared to healthy controls, with approximately one-third of people with epilepsy reporting a sleep disturbance [30]. Up to half of children with newly diagnosed epilepsy have sleep disturbances at the time of diagnosis, suggesting an underlying common mechanism or a link with seizures themselves [31]. In fact, sleep disturbances are less evident when seizures are well-controlled [32].

Insomnia is common in people with epilepsy, with an estimated prevalence of up to 50% [30]. Moreover, about 10–35% of people with epilepsy suffer from comorbid obstructive sleep apnea (OSA), with significantly higher incidence in those with refractory
Table 1
Wake- and sleep-promoting mechanisms in the brain (adapted from [12]).

| Anatomical region | Main Neurotransmitters | Connections (see [12] for details of original studies) | Description of findings |
|--------------------|------------------------|--------------------------------------------------------|-------------------------|
| **Predominantly wake-promoting areas** | | | |
| **Brainstem** | | | |
| Dorsal and median raphe nuclei | Serotonin Dopamine GABA Glutamate | The dorsal raphe nucleus in primates contains the largest number of 5-HT neurons in the brain. These neurons project to all basal ganglia nuclei as well as to the thalamus, hypothalamus, basal forebrain, limbic system, brainstem, and cerebral cortex. | Firing of serotonergic neurons in dorsal raphe is highest in waking, lower in NREM and almost absent in REM, and serotonin levels in brain are higher in waking than sleep and REM. However, serotonin receptor subtypes may have opposite effects on wake and sleep, selective serotonin uptake inhibitors have variable effects on wake and sleep, and some serotonergic dorsal raphe neurons fire during sleep. Lesioning the raphe nuclei had sleep-promoting effects, this may be due to the effect of serotonin-induced hypothermia on sleep. Dorsal raphe dopamine neurons promote waking. |
| Locus coeruleus (LC) | Noradrenaline | Noradrenergic neurons from the LC innervate the entire CNS including basal ganglia. The end-organ effects are modulated by differences in peptide expression and receptors. | LC neurons fire steadily during sleep; less during NREM and virtually silent during REM. Changes in LC activity precede EEG transitions from wake to NREM and NREM to waking. Optogenetic stimulation of LC causes sleep to wake transitions. However, lesions of LC do not produce consistent changes in EEG or behavioral arousal and genetic ablation of the NE precursor dopamine decarboxylase does not affect sleep-wake states. |
| Ventral tegmental area (VTA) | Dopamine GABA Glutamate | Cerebral cortex, basal forebrain, hypothalamus, basal ganglia, limbic system, brainstem. | Activity of VTA dopamine neurons higher in waking and REM compared to NREM, inhibition of their activity increases sleep characteristic. |
| Pedunculopontine-tegmental nucleus (PPT) / laterodorsal nucleus (LDT) | Acetylcholine GABA Glutamate | The PPT contains cholinergic, GABAergic and glutamatergic neurons which project to the striatum, globus pallidus, STN, SNc, thalamus, hypothalamus, basal forebrain, pontine and medullary reticular formation, spinal cord, cerebellum and cerebral cortex. Major afferents to the PPT originate in the basal ganglia with projections from the GPi, STN and SNr. It also receives input from the orexin neurons of the hypothalamus, histaminergic neurons from the TMN, serotonergic input from the dorsal raphe, adrenergic input from the LC, and cholinergic input from the LDT and contralateral PPT. | Cholinergic and some GABAergic and glutamatergic neurons in the PPT/LDT fire maximally during waking and REM. Some GABAergic and glutamatergic neurons only fire in REM. Some glutamatergic neurons are active in waking only. Chemogenetic activation of PPT glutamatergic neurons increased waking time, cholinergic neurons had no effect on waking/sleep time but reduced slow waves in NREM sleep, GABAergic neurons slightly reduced REM sleep. Optogenetic stimulation of cholinergic PPN and LDT neurons induced REM from NREM. Lesioning the PPT does not have substantial effects on sleep-wake architecture. Chemogenetic activation of PB-extra thalamic (but not thalamic pathway) leads to increase in wakefulness |
| Parabrachial nucleus (PB) | Glutamate Dopamine | Basal forebrain, intralaminar thalamus, lateral hypothalumus, amygdala, dorsolateral and medial prefrontal and insular cortex, VLPO | Cholinergic and some GABAergic and glutamatergic neurons only fire in REM. Some glutamatergic neurons in the PPT/LDT fire maximally during waking and REM. Some GABAergic and glutamatergic neurons only fire in REM. Some glutamatergic neurons are active in waking only. Chemogenetic activation of PPT glutamatergic neurons increased waking time, cholinergic neurons had no effect on waking/sleep time but reduced slow waves in NREM sleep, GABAergic neurons slightly reduced REM sleep. Optogenetic stimulation of cholinergic PPN and LDT neurons induced REM from NREM. Lesioning the PPT does not have substantial effects on sleep-wake architecture. Chemogenetic activation of PB-extra thalamic (but not thalamic pathway) leads to increase in wakefulness |
| Ventral Stream of ARAS | Acetylcholine GABA Glutamate | The basal forebrain receives afferents from a large area of the brainstem tegmentum including ventral tegmental area, substantia nigra, retrorubral field, raphe nuclei, reticular formation, PPN, LDT, PB and LC. Efferent fibres go to the amygdala, hippocampus, olfactory bulb, cerebral cortex | Basal forebrain neurons are active in waking and REM but not in NREM sleep. Chemogenetic activation of BF GABAergic neurons facilitates wakefulness. Cholinergic, glutamatergic and parvalbumin (PV)-positive GABAergic neurons were more active during wake and REM whereas somatostatin (SOM)-positive GABAergic neurons were active during NREM. Optogenetic activation of cholinergic and glutamatergic caused transition from NREM to wakefulness and desynchronization of the EEG. PV + GABAergic neurons promoted waking and SOM + GABAergic activation promoted NREM. Cholinergic neurons are active during waking states and silent during NREM and REM sleep. Optogenetic silencing of TMN histaminergic neurons promotes NREM sleep. Non-selective activation of preoptic GABA and glutamatergic neurons causes increase in waking. |
| Tuberomammillary nucleus | Histamine GABA | Cerebral cortex, thalamus, hypothalamus, basal forebrain, septum, olfactory bulb, amygdala, hippocampus, basal ganglia, brainstem, spinal cord. | Firing of serotonergic neurons in dorsal raphe is highest in waking, lower in NREM and almost absent in REM, and serotonin levels in brain are higher in waking than sleep and REM. However, serotonin receptor subtypes may have opposite effects on wake and sleep, selective serotonin uptake inhibitors have variable effects on wake and sleep, and some serotonergic dorsal raphe neurons fire during sleep. Lesioning the raphe nuclei had sleep-promoting effects, this may be due to the effect of serotonin-induced hypothermia on sleep. Dorsal raphe dopamine neurons promote waking. |
| Preoptic hypothalamus | GABA | Hypothalamic nuclei, brainstem nuclei (dorsal raphe, LC, ventrolateral medulla, parabrachial nucleus), TMN, amygdala, cerebral cortex, claustrum. | Firing of serotonergic neurons in dorsal raphe is highest in waking, lower in NREM and almost absent in REM, and serotonin levels in brain are higher in waking than sleep and REM. However, serotonin receptor subtypes may have opposite effects on wake and sleep, selective serotonin uptake inhibitors have variable effects on wake and sleep, and some serotonergic dorsal raphe neurons fire during sleep. Lesioning the raphe nuclei had sleep-promoting effects, this may be due to the effect of serotonin-induced hypothermia on sleep. Dorsal raphe dopamine neurons promote waking. |

(continued on next page)
to trigger or aggravate OSA in 28–57% of patients [42–44], possibly where its prevalence might reach 89% [38]. OSA appears to be more frequent in older patients and in late-onset epilepsy [43]. This syndrome favored by reduced exercise and weight-gaining ASMs prevalence of OSA in epilepsy, including a higher rate of metabolic pressure (CPAP) treatment is associated with reduced seizure [39], in particular nocturnal GTCS, while continuous positive airway pressure is often depicted by the cyclic alternating pattern [CAP] and by unstable phases of sleep, characterized by arousal fluctuations (vicious circle) [51,54]. Arousal fluctuations may increase seizure susceptibility and seizures may further increase with centrotemporal spikes, Landau–Kleffner syndrome, electrical status epilepticus during slow-wave sleep and sleep-related hyperarousal (SUDEP) may be associated in some cases with an increase in seizures [33–37]. In a recent series of 255 consecutive patients with epilepsy undergoing video-EEG monitoring and concomitant polysomnography, 26% had moderate-to-severe OSA [33]. OSA appears to be more frequent in older patients and in late-onset epilepsy [33,38], where its prevalence might reach 89% [38]. OSA appears to be more frequent in older patients and in late-onset epilepsy [33,38]. Several factors might contribute to an increased prevalence of OSA in epilepsy, including a higher rate of metabolic syndrome favored by reduced exercise and weight-gaining ASMs such as valproate [41]. Vagus nerve stimulation (VNS) also appears to trigger or aggravate OSA in 28–57% of patients [42–44], possibly through a stimulation-induced left vocal cord adduction [43]. This issue can be usually controlled by adjusting VNS therapy or OSA treatment [44].

Excessive daytime sleepiness occurs in 11–34% [30] and restless leg syndrome (RLS) in 13% of people with epilepsy [29]. All of these disorders are about twice as common in people with epilepsy than in control [45,46], from an odds ratio of 1.7 for insomnia up to 4.7 for RLS in epilepsy patients vs controls. Quality of life is lower in people with epilepsy than in people without epilepsy across all domains, and also significantly lower in people with epilepsy who have sleep problems than in people with epilepsy without sleep problems [47]. It is hence clear that sleep problems further worsen quality of life, in addition to the impact of epilepsy itself, highlighting the importance of identifying and treating these disorders.

### 1.2.2. Impact of sleep and sleep disorders on seizures and risk of SUDEP

In some individuals and in particular syndromes, distinct sleep physiology may reveal, and possibly also promote, a variety of interictal epileptiform discharges (IEDs) and ictal events. Similarly, NREM sleep has in the past been associated with more frequent IEDs and seizures than REM sleep [48–50]. In particular, both IEDs and seizures have been reported to occur more frequently during unstable phases of sleep, characterized by arousal fluctuations (visually depicted by the cyclic alternating pattern [CAP] and by quantified EEG analyses) [51–53]. Arousal fluctuations may increase seizure susceptibility and seizures may further increase arousal fluctuations in a vicious circle [51,54].

Epilepsy syndromes promoted by sleep include benign epilepsy with centrotemporal spikes, Landau–Kleffner syndrome, electrical status epilepticus during slow-wave sleep and sleep-related hypomotor epilepsy [55]. On the other hand, sleep deprivation is associated with a significant increase in cortical excitability [56], is commonly used to promote the occurrence of interictal epileptiform discharges during EEG recordings [57], and may favor seizure...
occurrence [58], although this may not always be the case (see [59]).

Two-thirds of sudden unexpected deaths in epilepsy patients (SUDEP) occur in bed, usually at night, during sleep, in a person not sharing their bedroom [60]. Furthermore, 73% of SUDEP recorded in epilepsy monitoring units occurred in patients suffering a GTCS at night while sleeping [61]. Accordingly, the presence of nocturnal GTCS and not sharing a bedroom are among the greatest SUDEP risk factors [60]. Up to 70% of SUDEP patients are found deceased while lying in the prone position, suggesting that this position directly contributes to the respiratory failure observed in most SUDEP [60,61]. Comorbid OSA might also be a risk factor for SUDEP [37], though this remains to be authoritatively demonstrated.

1.2.3. Impact of seizures on sleep (sleep fragmentation)

Sleep architecture is affected in people with epilepsy, not only as a direct result of nocturnal seizures. In juvenile myoclonic epilepsy (JME), sleep architecture shows reduced sleep efficiency, reduced percentage of non-REM sleep, reduced time in REM sleep, and increased time awake compared with controls [62–64]. In focal epilepsy, reduction of REM sleep is seen, increased duration but increased fragmentation of slow-wave sleep and increased time awake after sleep onset [65,66]. Overall, these features result in disturbed sleep and increased excessive daytime sleepiness, measured on one study as increased daytime sleep and nap frequency in people with intractable epilepsy compared with well-controlled epilepsy [67].

Impaired night-time sleep may increase the risk of day-time and night-time seizures in a vicious cycle of seizures and sleep disturbance that can result in psychiatric comorbidities and cognitive impairment in people with epilepsy, which globally decrease their quality of life as outlined above.

1.2.4. Impact of epilepsy treatment on sleep and alertness

The impact of ASMs on sleep and sleepiness is difficult to assess, as there are few randomized controlled studies using objective measures (e.g., polysomnography), and there are many confounders, such as polytherapy [68,69]. Although the bidirectional relationship between sleep and epilepsy is well known, current epilepsy management guidelines fail to account for the impact of ASM on sleep. The most recent systematic review and meta-analysis of randomized controlled trials that evaluated the impact of ASMs on polysomnographic parameters was based on 18 trials, not all of which were conducted in patients with an epilepsy diagnosis [69]. The effects of five groups of drugs (sodium-channel blockers; calcium-channel blockers; GABA enhancers; synaptic vesicle protein 2A [SV2A] ligands, and broad-spectrum medications) on slow-wave sleep (SWS), REM sleep, and sleep efficiency were analyzed [69].

The study findings suggest that GABA enhancers (data available for tiagabine) and calcium-channel blockers (carbamazepine), SV2A ligands (levetiracetam), and broad-spectrum ASMs did not affect SWS, REM sleep, or sleep efficiency [69]. However, it is currently impossible to translate these findings into authoritative pragmatic advice on choice of ASMs for people with epilepsy and to date the impact of ASMs on sleep remains poorly investigated in people with epilepsy [70].

Previous systematic reviews [71,72] and individual studies suggest that some ASMs may induce sleep fragmentation (increase of light sleep and wakefulness after sleep onset, reduction of N3 and REM sleep) [73], while others have a neutral or positive effect on sleep, either directly or indirectly through clinical and electrographic improvement of epilepsy [30,68,71–75]. Barbiturates and phenytoin appear to have mainly adverse effect on nocturnal sleep and increase daytime somnolence [71,73,76–79]. The impact of benzodiazepines on sleep remains similarly poorly investigated in epilepsy and some of its effects might be beneficial, especially when dosing and comorbidities (i.e., sleep apnea and circadian rhythm disorder) are taken into account [80].

Studies with carbamazepine suggest detrimental effects on sleep macrostructure and microstructure in people with epilepsy [71,79]. However, findings remain inconsistent across studies and, for example, Cho et al. [81] described an increase of N3 in new-onset focal epilepsy induced by low dose of controlled release carbamazepine, and Legros and Bazil reported no sleep effects of carbamazepine in a parallel monotherapy study [77]. Similarly, Jain and Glausier (2014) in their evidence-based review of objective sleep metrics of various epilepsy treatments suggest that carbamazepine may act to promote N3, with minimal effect of total sleep time [71].

Studies with valproic acid have produced conflicting data [71,63,82], with more recent studies possibly suggestive of a beneficial effect on sleep macrostructure and microstructure (cyclic alternating pattern) with valproate in adult patients with JME [63,82].

Daytime sleepiness has been commonly reported with older ASMs (e.g., carbamazepine, phenobarbital, and valproate) [71,75], especially with higher doses and polytherapy [74].

To date, there is limited evidence to support any significant modifying effects of levetiracetam, topiramate, zonisamide, and lacosamide on sleep architecture [81,83–86]. Association of a negative effect on sleep quality for some ASMs, such as topiramate, may result from an increased individual susceptibility to develop or to worsen patients’ existing sleep related movement disorder such as RLS and periodic limb movement disorder [87–90].

Given the bidirectional relationship between sleep and epilepsy, it is perhaps unsurprising that several ASMs have been also reported to improve sleep in people with epilepsy. For example, improvements in sleep quality or sleep structure have been documented with lamotrigine (REM sleep increase), gabapentin (SWS increase), pregabalin (SWS increase, improved sleep continuity), perampanel (SWS increase, decrease of wakefulness after sleep onset), and eslicarbazepine (less sleep instability in cyclic alternating pattern [CAP] parameters) [91–97]. It is worth mentioning that, while in the past lamotrigine was infrequently associated with insomnia [98], a more recent study on insomnia in people with epilepsy did not find an increased prevalence of insomnia in patients treated with lamotrigine [99]. Table 2 summarizes currently understood effects of ASMs on sleep and sleep disorders.

Other treatment modalities have also been shown to impact sleep in people with epilepsy. For example, neurosurgical treatment has been associated with improved sleep architecture in mesial temporal lobe epilepsy [100] and in drug-refractory patients [101]. Similarly, VNS seems to reduce daytime sleepiness when used at low intensities but may cause sleep fragmentation (increase of arousal index and of wakefulness after sleep onset) and increase daytime sleepiness at higher intensities [102–104]. A correlation between arousal index and voltage of deep-brain stimulation of anterior thalamus in drug refractory epilepsy was found in a small case series [105]. Lastly, a single study on the ketogenic diet showed improved sleep quality (decrease total sleep time, reduced N2, and increased REM sleep) in children with refractory epilepsy [106].

1.2.5. Effects of stimulants on sleep in people with epilepsy

There have been different clinical schools of thought about the appropriate use of stimulants for fatigue and excessive daytime sleepiness in a variety of neurological disorders, including epilepsy. Although fatigue and excessive daytime sleepiness are common problems in people with epilepsy, concerns have been raised over the increased risk of seizures during stimulant use [107].
Modafinil, a relatively widely used stimulant and wake-promoting drug, is thought to increase vigilance by modifying brain dopaminergic signals via inhibition of dopamine reuptake, possibly via the same binding site as cocaine [108]. A retrospective chart review of patients with epilepsy and other comorbidities who were given modafinil over ten years showed no relationship between seizures and dose of modafinil [107]. In only 6 of 205 patients, modafinil was discontinued due to concerns of seizure exacerbation, with 4 patients recorded as developing de novo seizures following modafinil initiation. Notably, no major exacerbation of seizures was seen in patients with epilepsy as their sole neurological condition, even in patients who were on ASM polytherapy [30].

Apart from modafinil, two other stimulants have been considered for use in people with epilepsy: pitolisant and solriamfetol. Of the two, only pitolisant has some available data on its effects in patients with epilepsy. Pitolisant belongs to a new class of drugs, the nonimidazole histamine H 3 receptor antagonists [109], which may have additional antiepileptic properties. Pitolisant is an H 3 receptor antagonist and inverse agonist [109], and findings of one study suggest that it may be effective in suppressing epileptiform discharges and concomitant myoclonic jerks in patients with epilepsy with a photoparoxysmal EEG response [110]. However, an exploratory phase II study, which evaluated the safety and anti-seizure effects of pitolisant, failed to show the efficacy in refractory focal epilepsy [111].

To date, there is no experimental or clinical data on use of solriamfetol in people with epilepsy. However, given its increasingly recognized beneficial effects on excessive daytime sleepiness in narcolepsy and OSA [112], future studies are warranted to gauge its potential role in managing sleepiness in people with epilepsy.

1.3. Assessing sleep

The goal of the diagnostic workup is twofold: diagnosing sleep-related epilepsy and diagnosing sleep disorders as comorbid conditions in people with epilepsy, as outlined in a recently published consensus review of a joint working group of the European Academy of Neurology (EAN), European Sleep Research Society (ESRS) and the International League Against Epilepsy – Europe [7]. The main elements of the diagnostic workup are summarized in Table 3.

1.3.1. Suspicion of sleep-related epilepsy

Clinical history is the starting point in the diagnostic workup for sleep-related epilepsy; refer to the consensus review for more detail [7]. Important aspects include: semiology of the nocturnal paroxysmal episodes; circumstances under which they occurred; timing and circadian distribution; frequency across the night and over time; clusters of episodes; evolution of the disorder over time; response to previous treatments; and personal and family medical history, not only of epilepsy but also regarding comorbidities [7]. It is crucial to obtain information from a bed partner or other witnesses. Questionnaires [113–115] and home video recordings have high diagnostic value [115], and the gold standard for diagnosing sleep-related epilepsy is video-EEG-PSG recording [7].

1.3.2. Suspicion of comorbid sleep disorders

Sleep deprivation as a consequence of comorbid sleep disorders in people with epilepsy may interfere with seizure control [30]. The recent European consensus review [7] focused on the most common conditions: sleep disordered breathing (including OSA), insomnia and RLS. The diagnostic approach and criteria are accord-
ing to the ICSD-3. Parasomnias were not considered in the consensus review, as they deserve a specific analysis particularly relating to differential diagnoses.

In people with epilepsy, it is important to ask about daytime sleepiness, fatigue, and non-restorative sleep. These symptoms may be caused by ASMs as well as seizures; however, the possibility of sleep disorders causing or aggravating these symptoms should be considered. History of witnessed snoring, apneas, overweight patient, and facial dysmorphisms should raise the suspicion of comorbid SDB and lead to further investigations. Several questionnaires have been developed to improve diagnostic accuracy of SDB, insomnia and RLS. The vast majority are not validated for people with epilepsy (none for sleep-related epilepsy).

Clinical practice guidelines define the general indications for diagnostic tests when sleep disorders are suspected: actigraphy, home sleep testing, and polysomnography, and the same indications apply for people with stable epilepsy as for people without epilepsy [7]. In people with non-stable forms of epilepsy, inpatient or ambulatory video-PSG with extended EEG cover are considered appropriate to diagnose SDB and other comorbid sleep disorders as well as unreported nocturnal epileptic seizures contributing to sleep disruption.

2. Methods

In view of the lack of published evidence, the Delphi method was used to establish a consensus on how to identify and manage sleep disorders in epilepsy. A Delphi technique uses an iterative multistage process where a group of experts anonymously answer a number of non-hierarchical statements that are subsequently amended/reworded until a group consensus is reached. The initial statements were developed by one of the authors (SB). The other authors were subsequently asked to either agree with each statement or provide an alternative statement if disagreeing. The statements in which consensus was not reached were rephrased and the process repeated until consensus (i.e., more than 5 of the 6 authors) had been reached for all statements. To avoid bias, replies were only seen by the author responsible for the wording of the statements. A total of three rounds of the process were performed. Consensus was reached for 15/19 statements after the first round, 18/19 after the second round, and 19/19 after the third round.

3. Recommendations

3.1. Identifying sleep disorders and sleep disturbances in people with epilepsy

See Fig. 1 for an algorithm summarizing the recommendations for identifying sleep problems in people with epilepsy. A detailed clinical history of sleep-related habits, sleep hygiene, and any other behavioral factors that can have a negative effect upon sleep wake rhythms should be obtained from all patients with epilepsy and their bed partners, even when no overt sleep-related complaints are present. The clinical history taking for assessing quality of sleep should start with open questions on general aspects of disturbed or non-restorative sleep and daytime sleepiness. In cases with positive findings in the open questions, more focused questions should follow. A set of screening questions targeting major comorbid sleep disorders (such as OSA and RLS) should be obtained from patients with epilepsy and their bed partners, when there is any indication in the open questions and early part of the history that there is any issue.

Fig. 1. Algorithm for identifying sleep disorders and problems in people with epilepsy. ICSD-3, International Classification of Sleep Disorders version 3; PSG, MSLT, multiple sleep-latency test; OSA, obstructive sleep apnea; polysomnography; RLS, restless leg syndrome. *First diagnostic contact should be with a neurologist, pediatrician, child neurologist, or epileptologists. The second diagnostic contact should be with a sleep physician with interest in epilepsy. **Diaries can help to record clinical details in a standardized way. Formal screening tools may be useful, but note that few questionnaires for sleep disorders have been validated for use in people with epilepsy. °Clinical practice guidelines define the indications for diagnostic tests when sleep disorders are suspected; the same indications apply for people with epilepsy. See Nobili et al. [7] for details. ¶Manage sleep disorder as per relevant guidelines for that sleep disorder. Management of the most complex cases should be transferred to specialized sleep centers. "Stimulants may have a potential to lower seizure threshold and increase the risk of uncontrolled or breakthrough seizures and risks benefits need to be reviewed when considering starting these drugs in people with epilepsy.
To streamline the identification of epilepsy patients with potential sleep disturbances, questions could be added to standard intake forms (e.g., to record sleep/wake times, duration of sleep, and any signs of disrupted sleep or sleep disorders; Box 1)

**Box 1**
Suggested questions to include in standard intake forms

**Recommended intake questions**

1. What time do you go to bed and what time do you get up?
2. How many hours do you think you sleep per night?
3. Do you snore regularly?
4. Has anyone noticed that you stop breathing during sleep?
5. Do you feel sleepy during the day?
6. Do you have difficulty in falling asleep? Do you wake up often during the night?
7. Do you struggle to get up in the morning? Do you feel refreshed when you wake up?
8. Has anyone noticed you moving your legs often in your sleep or other unusual behaviors?

These questions should be used as a quick clinical aid to direct further investigation, also on the basis of the patient’s clinical epilepsy-related symptoms.

Questionnaires and diaries could facilitate recording of clinical details in a standardized way in case of suspicion of comorbid sleep disorders. However, only a few have been validated in people with epilepsy and the expert consensus recommendation [7] was that the use of these in clinical practice should be optional.

In people with epilepsy and suspected comorbid sleep disorders, appropriate diagnostic investigations should be performed (e.g., actigraphy, ambulatory or laboratory polysomnography (PSG/Video-PSG), Multiple Sleep Latency Test). The indication for each test should be the same as for people without epilepsy. Patients with sleep-related epilepsy and uncontrolled seizures should be investigated with home sleep studies or inpatient video-PSG (full 10–20 electrode set) in case of a suspicion of a sleep disorder.

The first diagnostic contact should be with a neurologist, pediatrician, child neurologist, or epileptologist. The second diagnostic contact should be with a sleep physician with interest in epilepsy, and management of the most complex cases should be transferred to specialized sleep centers.

### 3.2. Managing excessive daytime sleepiness

See Fig. 2 for an algorithm to guide management of excessive daytime sleepiness in people with epilepsy. For people with excessive daytime sleepiness (i.e., Epworth sleepiness score > 10), clinicians should ensure patients have good sleep hygiene and adequate sleep opportunity. A psychoeducational approach should be applied to inform patients about habits or practices that may negatively impact their sleep and vigilance levels, and to implement strategies (“sleep hygiene rules”) for avoiding them (Box 2). Wherever possible, nationally approved sleep hygiene educational leaflets and digital resources should be made available or recommended during initial consultations.

**Box 2**
Ten rules for improved sleep hygiene (Adapted from [123])

**Sleep hygiene**

1. Try to keep regular times for going to bed and getting up. Set a bedtime that is early enough for you to get at least 7 hours of sleep.
2. Do not consume products containing stimulants, such as caffeine (tea, coffee, cocoa, chocolate, soft drinks, etc.), at least 4 hours before bedtime.
3. Avoid nicotine (including nicotine patches or chewing gum, etc.), which is also a stimulant, an hour before bedtime and when waking at night.
4. Avoid alcohol around bedtime because although it can promote sleep at first, it can disrupt sleep later in the night.
5. Avoid eating a large meal immediately before bedtime, although a light snack may be beneficial.
6. Try to do regular physical exercise if you are able, but avoid doing this in the 2 hours before bedtime.
7. Keep the bedroom calm and tidy. Select a mattress, sheets, and pillows that are comfortable.
8. Avoid making your bedroom too hot or too cold.
9. Keep the bedroom quiet and darkened during the night, but try to spend some time in daylight (or bright artificial light) during the day.
10. Keep your bedroom mainly for sleeping. Turn off electronic devices at least 30 minutes before bedtime.

The possible presence of sleep fragmentation induced by sleep-related seizures should be ruled out (if necessary, with video-PSG recording). Similarly, any sleep disorders that may fragment sleep and induce daytime sleepiness (OSA, central hypersomnias, periodic limb movement disorder, etc.) should be recognized and treated according to standard procedures.

As medication for epilepsy and other conditions may influence sleep and tiredness, the dose and timing of ASMs should be optimized to avoid daytime sedation (e.g., taking sedative drugs or their highest daily dosage before bedtime). If excessive daytime sleepiness persists even after optimization of dose and timing of ASMs, a switch to less sedating ASMs should be considered. Similarly, the dose and timing of any non-antiepileptic sedative drugs (anxiolytics, antidepressants, etc.) should be optimized to avoid daytime sedation (e.g., taking sedative drugs or their highest daily dosage before bedtime).

### 3.3. Managing poor night-time sleep

See Fig. 3 for an algorithm to guide management of insomnia in people with epilepsy. Sleep hygiene should be discussed and a psychoeducational approach should be applied to inform patients about habits or practices that may negatively impact their sleep and implement strategies (“sleep hygiene rules”) for avoiding them (Box 2). Wherever possible, nationally approved sleep hygiene...
Educational leaflets and digital resources should be made available, or recommended during initial consultations.

As for people with excessive daytime somnolence, the possible presence of sleep fragmentation induced by sleep-related seizures should be ruled out (if necessary, with video-PSG recording). Insomnia or other sleep disorders that may delay sleep onset or fragment sleep (RLS, periodic limb movement disorder, circadian rhythm sleep disorders, OSA, etc.) should also be recognized and treated according to standard procedures.

To facilitate overnight sleep, the dose and timing of ASMs should be optimized to favor sleep onset/sleep continuity. Modify the timing of, or reduce dosage of, more alerting ASMs before bedtime or consider switching to sedating ASMs before bedtime. Similarly, the dose and timing of any non-antiepileptic drugs that may induce insomnia (steroids, beta-blockers, diuretics, serotonin reuptake inhibitors, etc.) should be optimized.

4. Summary and conclusions

There is an overwhelming body of evidence that strongly supports the importance of regulated sleep management in people with epilepsy. Good quality sleep is pivotal for mental and physical health throughout the entire lifespan, and people with epilepsy suffer with increased risk of sleep alterations and excessive daytime somnolence. A proper sleep management plan should be in place to ensure patients get the necessary rest to improve their quality of life.
somnolence. Moreover, comorbid sleep disorders are known to reduce seizure control, and in turn, sleep alterations and daytime sleepiness can be exacerbated by seizures and by antiepileptic treatments. Nevertheless, despite this widely accepted clinical association, authoritative controlled clinical trials that could guide clinical practice are lacking, and future studies are urgently needed.

In order to address this clinical need, we here present a pragmatic set of recommendations for clinicians who work with people with epilepsy, based on the best available current body of work. Firstly, we recommend that a clinical evaluation of sleep habits and sleep hygiene (Box 2) should be incorporated in clinical practice, and as far as possible, always obtained from people with epilepsy and their bed partners (Fig. 1). Secondly we recommend that the possible presence of sleep fragmentation induced by sleep-related seizures should be ruled out, and when a comorbid sleep disorder is suspected that an appropriate diagnostic investigation and treatment should be performed. Finally, we suggest that the dose and timing of antiepileptic medications (Table 2) and other comedations should always be optimized in order to improve nocturnal sleep and avoid daytime sedation.

Acknowledgement and contributions

Medical writing support for the coordination and editing of this review was provided by Kate Carpenter and funded by Eisai Europe Ltd. The review article was suggested by LN, following an advisory board meeting on the topic of sleep and epilepsy, which was arranged and funded by Eisai Europe Ltd., and was attended by LN, SHE, MT, and AR.

LN, SB, SHE, AR, PR, MT, and IR drafted the introduction. SB coordinated the Delphi process for the recommendations. SHE wrote the methods and the recommendations. LN, SB, and IR drafted the discussion and summary, and all authors contributed. All authors approved the final version for submission.

Disclosures

SHE has received honoraria for educational activities and conference attendance from UCB Pharma, LincoPharma, Eisai and Fidia Pharma.

AR has received honoraria for educational activities and conference attendance from UCB Pharma, Eisai and Fidia Pharma.

LN has received honoraria for educational activities and conference attendance from Bioprojet, Eisai and Fidia Pharma.

IR has no relevant disclosures.

References

[1] Medic G, Wille M, Hemels ME. Short- and long-term health consequences of sleep disruption. Nat Sci Sleep 2017;9:151–61.

[2] Javaheiripour N, Shahboulpor N, Noori K, Zare M, Camilleri JA, Laird AR, et al. Functional brain alterations in acute sleep deprivation: an activation likelihood estimation meta-analysis. Sleep Med Rev 2019;46:64–73.

[3] Grandner MA, Hale L, Moore M, Patel NP. Mortality associated with short sleep duration: The evidence, the possible mechanisms, and the future. Sleep Med Rev 2010;14:191–203.

[4] Tobaldini E, Fiorelli EM, Solbiati M, Costantino G, Nobili L, Montano N. Short sleep duration and cardiometabolic risk: from pathophysiology to clinical evidence. Nat Rev Cardiol 2019;16:213–24. https://doi.org/10.1038/s41569-018-0109-6.

[5] Uehli K, Mehta AJ, Mehto L, Zhong J, Magalhaes D, cereal A, et al. Sleep problems and work injuries: a systematic review and meta-analysis. Sleep Med Rev 2014;18:61–73.

[6] Institute of Medicine (US) Committee on Sleep Medicine and Research. Sleep Disorders and Sleep Deprivation: An Unmet Public Health Problem. Washington (DC): National Academies Press (US); 2006.

[7] Nobili L, Weerd A de, Rubolli G, Beniczky S, Derry C, Ericsson S, et al. Standard procedures for the diagnostic pathway of sleep-related epilepsies and comorbid sleep disorders: an EAN, ESRS and ILAE-Europe consensus review. Eur J Neurol nd. S. (2017). [https://doi.org/10.1111/ejn.14468].

[8] Gibson FM, Maccormac E, Gringras P. Sleep and epilepsy: unfortunate bedfellows. Arch Dis Child 2019;104:189–92.

[9] Kataria L, Vaughn BV. Sleep and epilepsy. Sleep Med Clin 2016;11:609–20.

[10] Rattenborg NC, de la Iglesia HO, Kempenaers B, Lesku JA, Meierlo P, Scriba MF. Sleep research goes wild: new methods and approaches to investigate the evolution, ecology and functions of sleep. Philos Trans R Soc Lond B, Biol Sci 2017;372.

[11] Le Bon O. Relationships between REM and NREM in the NREM-REM sleep cycle: a review on competing concepts. Sleep Med 2020;70:6–16.

[12] Chasegawa H, Selway R, Gnoor V, Beniczky S, Williams SCR, Kruger M, et al. The subcortical belly of sleep: New possibilities in neumodulation of basal ganglia?. Sleep Med Rev 2020;52:103137.

[13] Tononi G, Cirelli C. Sleep and synaptic down-selection. Eur J Neurosci 2020;51:413–21.

[14] Xie L, Kang H, Xu Q, Chen MJ, Liao Y, Thiyagarajan M, et al. Sleep drives metabolic clearance from the adult brain. Science 2013;342:373–7.

[15] Amici R, Bastarnani S, Bertotti C, Cerri M, Del Vecchio F, Lo Martire V, et al. Sleep and bodily functions: the physiological interplay between body homeostasis and sleep homeostasis. Arch Ital Biol 2014;152:66–78.

[16] Simor P, van der Wijk G, Nobili L, Peigné P. The microstructure of REM sleep: Why phasic and tonic?. Sleep Rev Med 2020;52:103105.

[17] Halasz P, Boduzs R, Ujma PP, Fabi D, Szics A. Strong relationship between NREM sleep, epilepsy and plastic functions - A conceptual review on the neurophysiology background. Epilepsy Rev 2019;150:95–105.

[18] Scammell TE, Arrigoni E, Lipton JO. Neural circuitry of wakefulness and sleep. Neuron 2017;93:747–65.

[19] Tononi G, Cirelli C. Sleep function and synaptic homeostasis. Sleep Med Rev 2006;10:49–62.

[20] Diekemann S, Born J. The memory function of sleep. Nat Rev Neurosci 2005;6:513–25.

[21] Saper CB, Fuller PM. Wake-sleep circuitry: an overview. Curr Opin Neurol Biol 2017;44:186–92.

[22] Polshek D, Gildeh N, Cash D, Winskys-Sommerer R, Williams SCR, Turkmener F, et al. Obstructive sleep apnoea and Alzheimer’s disease: in search of shared pathomechanisms. Neurosci Biobehav Rev 2018;86:142–9.

[23] Rechtschaffen A, Gilliland M, Bergmann B, Winter J. Physiological correlates of prolonged sleep deprivation in rats. Science 1983;221:184–4.

[24] Banks S, Dinger DF. Behavioral and physiological consequences of sleep restriction. J Clin Sleep Med 2007;3:519–28.

[25] CDC - Data and Statistics - Sleep and Sleep Disorders 2019. [https://www.cdc.gov/sleep/about_data/statistics.html] (accessed October 4, 2020).

[26] Hanseleit K, Hellhammer D, Behnert B, Ringelstein E, et al. National Sleep Foundation’s updated sleep duration recommendations: final report. Sleep Health 2015;1:233–43.

[27] Hossain JL, Shapiro CM. The prevalence, cost implications, and management of sleep disorders: an overview. Sleep Breath 2002;6:85–102.

[28] Gustavsson A, Svensson M, Jacobs F, Allgulander C, Alonso J, Beghi E, et al. Cost of disorders of the brain in Europe 2010. Eur Neuropsychopharmacol 2011;21:718–79.

[29] Lowe CJ, Safati A, Hall PA. The neurocognitive consequences of sleep restriction: a meta-analytic review. Neurosci Biobehav Rev 2017;80:586–604.

[30] Van Grolde EGA, Gutter T, de Weerd AW. Sleep disturbances in people with epilepsy: prevalence, impact and treatment. Sleep Med Rev 2011;15:357–68.

[31] Byars AW, Byars KC, Johnson CS, deGrauw TJ, Fastenau PS, Perkins S, et al. The relationship between sleep problems and neuropsychological functioning in children with first recognized seizures. Epilepsy Behav 2008;13:607–13.

[32] Unterberger I, Gabelia D, Prienschl M, Chea K, Hofer M, Högl B, et al. Sleep disorders and circadian rhythm in epilepsy revisited: a prospective controlled study. Sleep Med 2015;16:237–42.

[33] Sivathambam S, Farrand S, Chen Z, White EJ, Pattichis AA, Hollis C, et al. Sleep-disordered breathing among patients admitted for inpatient video-EEG monitoring. Neurology 2019;92:e194–204.

[34] Malow BA, Levy K, Marenur K, Bowes R. Obstructive sleep apnoea is common in medically refractory epilepsy patients. Neurology 2000;55:1002–7.

[35] Manni R, Terzaghi M, Arbasino C, Sartori I, Galimberti CA, Tartara A. Obstructive sleep apnea in a clinical series of adult epilepsy patients: frequency and features of the comorbidity. Epilepsia 2003;44:836–40.

[36] Phillips MCL, Costello CA, White EJ, Smit M, Carino J, Strawhorn A, et al. Routine polysomnography in an epilepsy monitoring unit. Epilepsy Res 2013;105:401–4.

[37] McCarter AR, Timm PC, Shepard PW, Sandness D, Luu T, McCarter SJ, et al. Obstructive sleep apnea in refractory epilepsy: a pilot study investigating frequency, clinical features, and association with risk of sudden unexpected death in epilepsy. Epilepsia 2013;54:1973–81.

[38] Maurusser A, De Toffol B, Praline J, Birohn J, Limouzin N. High incidence of obstructive sleep apnea syndrome in patients with late-onset epilepsy. Neuropsychol Clin Clin Neurophysiol 2017;47:55–61.

[39] Chjerkevik AM, Abu-Khaliil B, Malow BA. Obstructive sleep apnea is associated with seizure occurrence in older adults with epilepsy. Neurology 2007;69:1823–7.

[40] Vendrume M, Auerbach S, Loddenkemper T, Rothare S, Montouris G. Effect of continuous positive airway pressure treatment on seizure control in patients with obstructive sleep apnea and epilepsy. Epilepsia 2011;52:e168–171.
[41] Soylemez E, Ozturk O, Baslo SA, Balgic ZE, Atakli D. Metabolic syndrome and obstructive sleep apnea syndrome among patients with epilepsy on monotherapy. Epilepsy Behav 2020;111:107290.

[42] Macies M, Edwards KA, Cheyer O, Tirmes G, Malow BA. Effects of vagus nerve stimulation on sleep-related breathing in epilepsy patients. Epilepsia 2003;44:930–5.

[43] Zanzmera P, Shukla G, Gupta A, Singh H, Goyal V, Srivastava A, et al. Markedly decreased sleep-related breathing disorders in adults with epilepsy. Epilepsy Behav 2018;79:126–9.

[44] Gammino M, Zumm L, Bue AL, Uroso L, Terruso V, Marrone O, et al. Excessive daytime sleepiness and sleep disorders in a population of patients with epilepsy: a case-control study. J Epilepsy Res 2016;6:79–86.

[45] Lin Z, Si Q, Xiaoyi Z. Obstructive sleep apnoea in patients with epilepsy: a meta-analysis. Sleep Breath 2017;21:263–70.

[46] Gutter T, Callenbach PMC, Brouwer OF, de Weerd AW. Prevalence of sleep disturbances in people with epilepsy and the impact on quality of life: a survey in secondary care. Seizure 2019;69:298–303.

[47] Ng M, Pavlova M. Why are seizures rare in rapid eye movement sleep? J Clin Neurophysiol 2000;17:191–8.

[48] Vanhatalo S, Palva JM, Holmes MD, Miller JW, Voipio J, Kaila K. Infraslow oscillations modulate excitability and interictal epileptic activity in the human cortex during sleep. Proc Natl Acad Sci U S A 2001;100:3053–7. https://doi.org/10.1073/pnas.0517101.

[49] Zubler F, Rubino A, Lo Russo G, Schindler K. Interictal correlating sleep with sigma and delta dynamics during non-rapid-eye-movement sleep. Front Neurol 2017;8:288. https://doi.org/10.3389/fneur.2017.00288.

[50] Gibbs SA, Proserpio P, Terzaghi M, Pigorini A, Sarasso S, Lo Russo G, et al. Sleep-related epileptiform behaviors and non-REM-related parasomnias: insights from Neurology-E. Sleep Med Rev 2016;25:4–20. https://doi.org/10.1016/j.smr.2015.05.009.

[51] Jin B, Aung T, Geng Y, Wang S. Epilepsy and its interaction with sleep and circadian rhythm. Front Neurol 2020;11:327.

[52] Badawy RAB, Curatolo JM, Newton M, Berkovic SF, Macdonell RAL. Sleep deprivation increases cortical excitability in epilepsy: syndrome-specific effects. Neurology 2006;67:1018–22.

[53] Giorgi FS, Guida M, Cacciagi L, Maestri M, Carnicelli L, Bonanni E, et al. Incidence of sleep deprivation increases cortical excitability in epilepsy: syndrome-specific effects. Neurology 2006;67:1018–22.

[54] Malow BA. Sleep deprivation and epilepsy. Curr Opin Neurol 2000;11:565–73.

[55] Pirlino R, Mifsud F, Nobili L. Sleep EEG: synchronization mechanisms and activation of interictal epileptic spikes. Clin Neurophysiol Off J Int Clin Neurophysiol Soc 2000;111:565–73.

[56] Pirlino R, Halasz F, Tassinari CA, Terzani MG. CAP, epilepsy and motor events during sleep: the unifying role of arousal. Sleep Med Rev 2006;10:267–85. https://doi.org/10.1016/j.smrv.2005.12.004.

[57] Vanhatalo S, Palva JM, Holmes MD, Miller JW, Voipio J, Kaila K. Infraslow oscillations modulate excitability and interictal epileptic activity in the human cortex during sleep. Proc Natl Acad Sci U S A 2001;100:3053–7. https://doi.org/10.1073/pnas.0517101.

[58] Zamboni P, Shukla G, Gupta A, Singh H, Goyal V, Srivastava A, et al. Markedly decreased sleep-related breathing disorders in adults with epilepsy. Epilepsy Behav 2018;79:126–9.

[59] Soylemez E, Ozturk O, Baslo SA, Balgic ZE, Atakli D. Metabolic syndrome and obstructive sleep apnea syndrome among patients with epilepsy on monotherapy. Epilepsy Behav 2020;111:107290.

[60] Macies M, Edwards KA, Cheyer O, Tirmes G, Malow BA. Effects of vagus nerve stimulation on sleep-related breathing in epilepsy patients. Epilepsia 2003;44:930–5.

[61] Zanzmera P, Shukla G, Gupta A, Pipolo G, et al. Laryngeal motility alteration: a missing link between sleep apnea and vagus nerve stimulation for epilepsy. Epilepsia 2016;57:e24–7.

[62] Salvadé A, Ryvlin P, Rossetti AO. Impact of vagus nerve stimulation on sleep-related breathing disorders in adults with epilepsy. Epilepsy Behav 2018;79:126–9.

[63] Gammino M, Zumm L, Bue AL, Uroso L, Terruso V, Marrone O, et al. Excessive daytime sleepiness and sleep disorders in a population of patients with epilepsy: a case-control study. J Epilepsy Res 2016;6:79–86.

[64] Lin Z, Si Q, Xiaoyi Z. Obstructive sleep apnoea in patients with epilepsy: a meta-analysis. Sleep Breath 2017;21:263–70.

[65] Gutter T, Callenbach PMC, Brouwer OF, de Weerd AW. Prevalence of sleep disturbances in people with epilepsy and the impact on quality of life: a survey in secondary care. Seizure 2019;69:298–303.

[66] Ng M, Pavlova M. Why are seizures rare in rapid eye movement sleep? J Clin Neurophysiol 2000;17:191–8.

[67] Vanhatalo S, Palva JM, Holmes MD, Miller JW, Voipio J, Kaila K. Infraslow oscillations modulate excitability and interictal epileptic activity in the human cortex during sleep. Proc Natl Acad Sci U S A 2001;100:3053–7. https://doi.org/10.1073/pnas.0517101.

[68] Zamboni P, Shukla G, Gupta A, Singh H, Goyal V, Srivastava A, et al. Markedly decreased sleep-related breathing disorders in adults with epilepsy. Epilepsy Behav 2018;79:126–9.

[69] Soylemez E, Ozturk O, Baslo SA, Balgic ZE, Atakli D. Metabolic syndrome and obstructive sleep apnea syndrome among patients with epilepsy on monotherapy. Epilepsy Behav 2020;111:107290.

[70] Romigi A, Cappellano S, Caccamo M, Testa F, Centonze D. The impact of antiseizure medications on polysomnographic parameters: a systematic review and meta-analysis. Sleep Med 2021. https://doi.org/10.1016/j.sleep.2021.02.056.
Insomnia is less prevalent and less severe, independent of depressive symptoms, in patients with epilepsy treated with perampanel as an adjuvant. Epilepsy Behav EB 2020;112:107384.

Sleep before and after temporal lobe epilepsy surgery. Seizure 2012;21:260–5.

Effect of successful epilepsy surgery on subjective and objective sleep parameters—a prospective study. Sleep Med 2013;14:333–8.

Vagus nerve stimulation reduces daytime sleepiness in epilepsy patients. Neurology 2001;57:879–84.

Daytime vigilance and quality of life in epileptic patients treated with vagus nerve stimulation. Epilepsy Behav EB 2003;4:185–91.

Modifications of sleep EEG induced by chronic vagus nerve stimulation in patients affected by refractory epilepsy. Clin Neurophysiol Off J Int Fed Clin Neurophysiol 2004;115:658–64.

Deep brain stimulation of anterior nucleus thalamus disrupts sleep in epilepsy patients. Epilepsia 2015;56:e99–e103.

Hallbök T, Lundgren J, Rosén I. Ketogenic diet improves sleep quality in children with therapy-resistant epilepsy. Epilepsia 2007;48:59–65.

Electrophysiological and amperometric evidence that modafinil blocks the dopamine uptake transporter to induce behavioral activation. Neuroscience 2013;252:118–24. https://doi.org/10.1016/j.neuroscience.2013.07.071.

Profile of pitolisant in the management of narcolepsy: design, development, and place in therapy. Drug Des Devel Ther 2018;12:2665–75. https://doi.org/10.2147/DDDT. S101145.

Collart Dutilleul P, Rychlin P, Kahane P, Verschuell M, Senah F, Biraben A, et al. Exploratory Phase II trial to evaluate the safety and the antiepileptic effect of pitolisant (BF2.649) in refractory partial seizures, given as adjunctive treatment during 3 months. Clin Neuropharmacol 2016;39:188–93. https://doi.org/10.1097/WNP.0000000000000159.

Abad VC. Profile of solriamfetol in the management of excessive daytime sleepiness associated with narcolepsy or obstructive sleep apnoea: focus on patient selection and perspectives. Nat Sci Sleep 2021;13:75–91. https://doi.org/10.2147/NSS.S45020.

Derry CP, Davey M, Johns M, Kron K, Clencoross D, Marini C, et al. Distinguishing sleep disorders from seizures: diagnosing bumps in the night. Arch Neurol 2006;63:705. https://doi.org/10.1001/archneur.63.5.705.

Manni R, Terzaghi M, Repetto A. The FLEP scale in diagnosing nocturnal frontal lobe epilepsy, NREM and REM parasomnias: data from a tertiary sleep and epilepsy unit. Epilepsia 2008;49:1581–5.

Velasco P, Busilni, C. Sleep in children with therapy-resistant epilepsy. Epilepsia 2007;48:59–65.

Abad VC. Profile of solriamfetol in the management of excessive daytime sleepiness associated with narcolepsy or obstructive sleep apnoea: focus on patient selection and perspectives. Nat Sci Sleep 2021;13:75–91. https://doi.org/10.2147/NSS.S45020.

Serafini A, Kuate C, Gelisse P, Velizarova R, Gigli GL, Coubes P, et al. Sleep and epilepsy unit. Epilepsia 2008;49:1581–5.