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Review

Expert Opinion: Managing sleep disturbances in people with epilepsy

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ABSTRACT

Poor sleep and daytime sleepiness are common in people with epilepsy. Sleep disorders can disrupt seizure control and in turn sleep and vigilance problems can be exacerbated by seizures and by antiepileptic treatments. Nevertheless, these aspects are frequently overlooked in clinical practice and a clear agreement on the evidence-based guidelines for managing common sleep disorders in people with epilepsy is lacking. Recently, recommendations to standardize the diagnostic pathway for evaluating patients with sleep-related epilepsies and comorbid sleep disorders have been presented. To build on these, we adopted the Delphi method to establish a consensus within a group of experts and we provide practical 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 should be always 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.

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 responsivity 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 recommen-

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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 exacerbating 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 then 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 awake, less during NREM and virtually silent during REM sleep. 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.
Parabrachial nucleus (PB)	Glutamate Dopamine	Basal forebrain, intralaminar thalamus, lateral hypothalamus, amygdala, dorsolateral and medial prefrontal and insular cortex, VLPO	Chemogenetic activation of PB-extra thalamic (but not thalamic pathway) leads to increase in wakefulness
Ventral Stream of ARAS			
Basal Forebrain (septal-diagonal complex, medial part of globus pallidus, magnocellular preoptic nucleus, substantia inominata)	Acetylcholine GABA Glutamate	The basal forebrain receives afferents from a large area of the brainstem tegmentum including ventral tegmental area, substantia nigra, retrorubal 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.
Tuberomamillary nucleus	Histamine GABA	Cerebral cortex, thalamus, hypothalamus, basal forebrain, septum, olfactory bulb, amygdala, hippocampus, basal ganglia, brainstem, spinal cord.	Histaminergic neurons are active during waking states and silent during NREM and REM sleep. Optogenetic silencing of TMN histaminergic neurons promotes NREM sleep.
Preoptic hypothalamus	GABA	Hypothalamic nuclei, brainstem nuclei (dorsal raphe, LC, ventrolateral medulla, parabrachial nucleus), TMN, amygdala, cerebral cortex, claustrum.	Non-selective activation of preoptic GABA and glutamatergic neurons causes increase in waking.

(*continued on next page*)

Table 1 (*continued*)

Anatomical region	Main Neurotransmitters	Connections (see [12] for details of original studies)	Description of findings
Lateral hypothalamus	Orexin	Cerebral cortex, basal forebrain, intralaminar and relay nuclei of the thalamus, basal ganglia, amygdala, many components of the ascending arousal system including the LC, dorsal raphe, parabrachial nucleus.	Orexin deficiency may lead to narcolepsy. Orexin neurons fire during waking and virtually cease to fire in NREM and REM sleep. Optogenetic stimulation of orexin neurons has a wake-promoting effect whereas silencing led to induction of NREM sleep.
Dorsal Stream of ARAS			
Thalamus (midline, intralaminar and reticular thalamic nuclei)	Glutamate GABA	Cerebral cortex, basal ganglia, amygdala, hippocampus, cerebellum, brainstem.	Stimulation of thalamic areas including the intralaminar nuclei leads to cortical recruiting response. Tracing studies show pathways from brainstem nuclei and reticular formation to thalamic midline and intralaminar nuclei. Thalamic reticular cells generate spindles. Chemogenetic activation of glutamatergic thalamocortical neurons had no effect on sleep-wake quantity, consolidation or sleep latency.
REM regulating areas			
Mesopontine tegmentum (ventrolateral periaqueductal gray and lateral pontine tegmentum) Sublaterodorsal nucleus (SLD) [subcoeruleus/peri-locus coeruleus alpha in cats] Precoeruleus region (see also PPT/LDT)	GABA Glutamate	Ventrolateral and lateral hypothalamus, septum, locus coeruleus, dorsal raphe nucleus, PPT, medial pontine and medullary reticular formation and spinal cord.	Selective lesions of the ventrolateral periaqueductal gray or lateral pontine tegmentum doubled the amount of REM sleep in rodents, lesions of the SLD produce reductions in REM and loss of atonia. Optogenetic stimulation of ventrolateral periaqueductal gray GABAergic neurons promoted REM – these neurons fired most during REM, least during NREM and variable rates during waking.
Predominantly sleep-promoting areas			
Lateral hypothalamus	Melanin concentrating hormone (MCH)	Medial septum, hippocampus, amygdala, basal forebrain, thalamus, hypothalamus, caudate, putamen, globus pallidus, periaqueductal gray, SNc, VTA, dorsal and median raphe nuclei, PPT/LDT, LC, pontine reticular formation.	MCH neurons are silent during waking, increase firing during NREM and fire more during REM. Optogenetic and chemogenetic activation of MCH neurons promotes REM. Silencing of MCH neurons do not have substantial effects on sleep-wake
Pre-optic hypothalamus	GABA Glutamate	TMN, dorsal raphe nucleus, LC, lateral hypothalamus, parabrachial nucleus), amygdala, cerebral cortex.	Optogenetic activation of preoptic GABAergic neurons projecting to the TMN increased NREM and REM sleep, inactivating them caused increased wakefulness and decreased NREM and REM sleep.

5-HT, 5-hydroxytryptamine; CNS, central nervous system; GABA, Gamma amino butyric acid; GPi, globus pallidus internus; LC, locus coeruleus; LDT, laterodorsal tegmental nucleus; MCH, melanin concentrating hormone; NE, norepinephrine; PB, parabrachial nucleus; OX-SAP, orexin-2-saporin conjugate; PPT, pedunculopontine-tegmental nucleus; REM, rapid eye movement; VTA, ventral tegmental area; SLD, sublaterodorsal nucleus; SNc, substantia nigra compacta; SNr, substantia nigra reticulata; STN, subthalamic nucleus; TMN, tuberomamillary nucleus; VLPO, ventrolateral preoptic nucleus.

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 likely to promote seizure occurrence in elderly patients [39], in particular nocturnal GTCS, while continuous positive airway pressure (CPAP) treatment is associated with reduced seizure frequency [40]. 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 hypermotor 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 Glauser (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].

Table 2
Summary of currently understood effects of ASMs on sleep and sleep disorders (adapted from [71,116] and updated).

ASM	Effects on sleep in epilepsy									Effects on sleep disorders	
	SE/TST	SL	WASO	N1	N2	N3	REM	Arousals	Sleep micro-structure	Improvement	Worsening
Phenobarbital [71,116]	↑	↓	–	–	↑	–	↓	↓	No data	Insomnia	OSA
Phenytoin [71,116]	–	↓	–	↑	↓	↓/↑	–/↓	–	No data	None	None
Carbamazepine [71,76,79,116]	–	–	–	–	–	↑	↓	↑	↑ CAP rate	RLS	NONE
Valproate [71,82,116]	–	–	–	↑	↓	–	–	–	↓ CAP rate	None	OSA*
Gabapentin [71,116,117]	–	–	–	–/↓	–	↑	↑	↓	No data	RLS	OSA*
Lamotrigine [71,98,116,118]	–	–	–	–	↑/–	↓/–	↑/–	–	No data	None	Insomnia
Topiramate [71,87–90,116]	–	–/↓	–	–	–	–	–	–	No data	OSA*	RLS PLMD†
Levetiracetam [71,116]	–	–	–	–	↑	↓	–	–	No data	None	None
Pregabalin [71,116,117]	↑	–	–	↓	–	↑	–	–	No data	RLS	OSA*
Zonisamide [71,119,120]	–	–	–	–	–	–	–	–	No data	OSA*	RLS†
Lacosamide [86]	–	–	–	–	–	–	–	↓	No data	None	None
Eslicarbazepine [96]	–	–	–	–	–	–	–	–	↓ CAP rate	None	None
Perampanel [99,121,122]	–	–	↓	–	–	↑	–	–	No data	Insomnia, RLS	None

*Due to weight change. †Few case reports.
–, No change; ↑, increase; ↓ decrease; CAP cyclic alternating pattern; OSA, obstructive sleep apnea; PLMD, periodic limb movement disorder; REM, rapid eye movement; RLS, restless leg syndrome; SE sleep efficiency; SL sleep latency; TST total sleep time; WASO wakefulness after sleep onset.

Table 3
Summary of the diagnostic workup for suspected sleep-related epilepsy (SRE) and suspected comorbid sleep disorders in people with epilepsy (Adapted from [7]).

1. Suspicion of SRE	2. Suspicion of comorbid sleep disorders
1.1 Clinical history	2.1 Clinical history
1.2 Questionnaires and diaries	2.2 Questionnaires and diaries
1.3 Tools for capturing the event at home:	2.3 Further diagnostic workup (tests)
1.3.1 Home-video recording	2.4 Management / treatment
1.4 Tools for objective evaluation in lab	
1.4.1 For capturing the event	
• overnight recording (video-EEG-PSG)	
1.4.2 For recording possible associated ictal/interictal abnormalities	
• daytime standard EEG	
• daytime sleep EEG	
• overnight recording with video-EEG-PSG	

EEG, electroencephalogram; PSG, polysomnography; SRE, sleep-related epilepsy.

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 [107].

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 receptors 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.

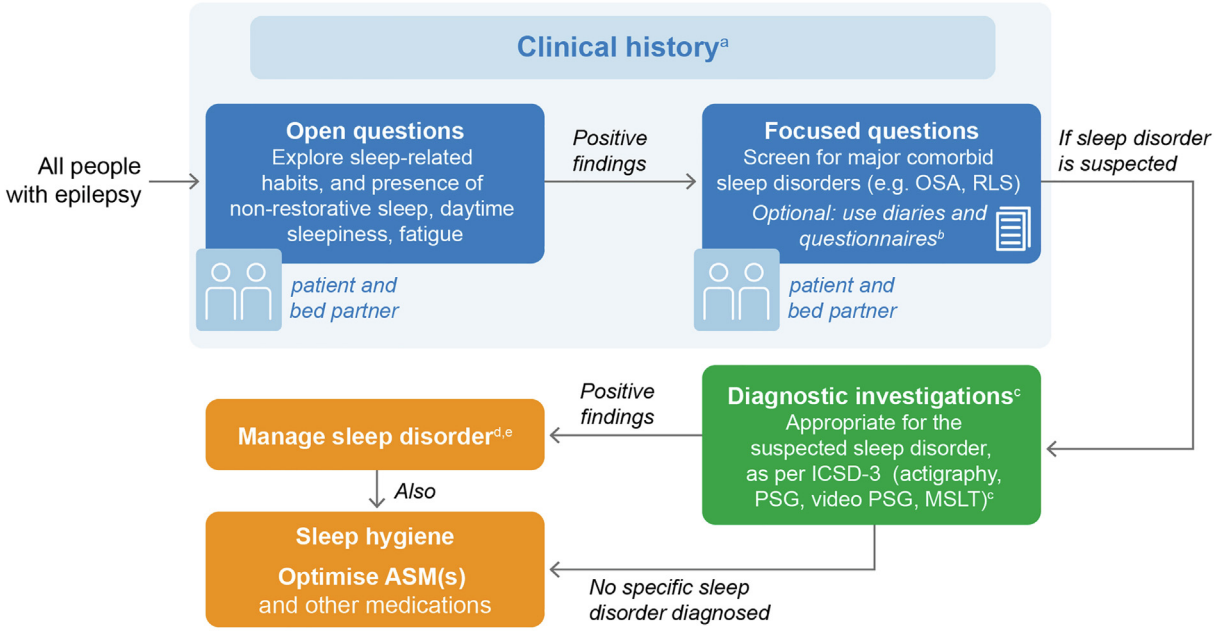

Fig. 1. Algorithm for identifying sleep disorders and problems in people with epilepsy. ICSD-3, International Classification of Sleep Disorders version 3; PSG, MSLT, multiple sleep-latency test; OSA, obstructive sleep apnea; polysomnography; RSL, restless leg syndrome. [a]First diagnostic contact should be with a neurologist, pediatrician, child neurologist, or epileptologists. The second diagnostic contact should be with a sleep physician with interest in epilepsy. [b]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. [c]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. [d]Manage sleep disorder as per relevant guidelines for that sleep disorder. Management of the most complex cases should be transferred to specialized sleep centers. [e]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

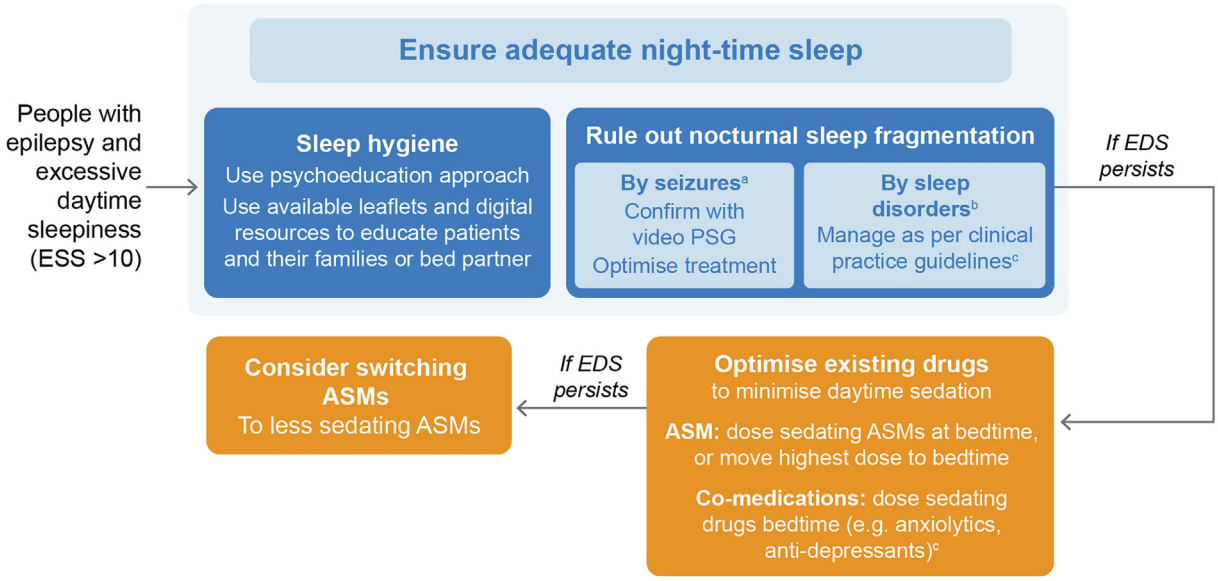

Fig. 2. Algorithm for managing excessive daytime sleepiness. EDS, excessive daytime sleepiness; PSG, polysomnography. [a]Refer to Nobili et al. [7] for diagnostic pathway for sleep-related epilepsies. [b]Such as sleep apnea, circadian rhythm sleep disorders, central hypersomnias, periodic limb movement disorder. Refer to Nobili et al. [7] for diagnostic pathway for comorbid sleep disorders. [c]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.

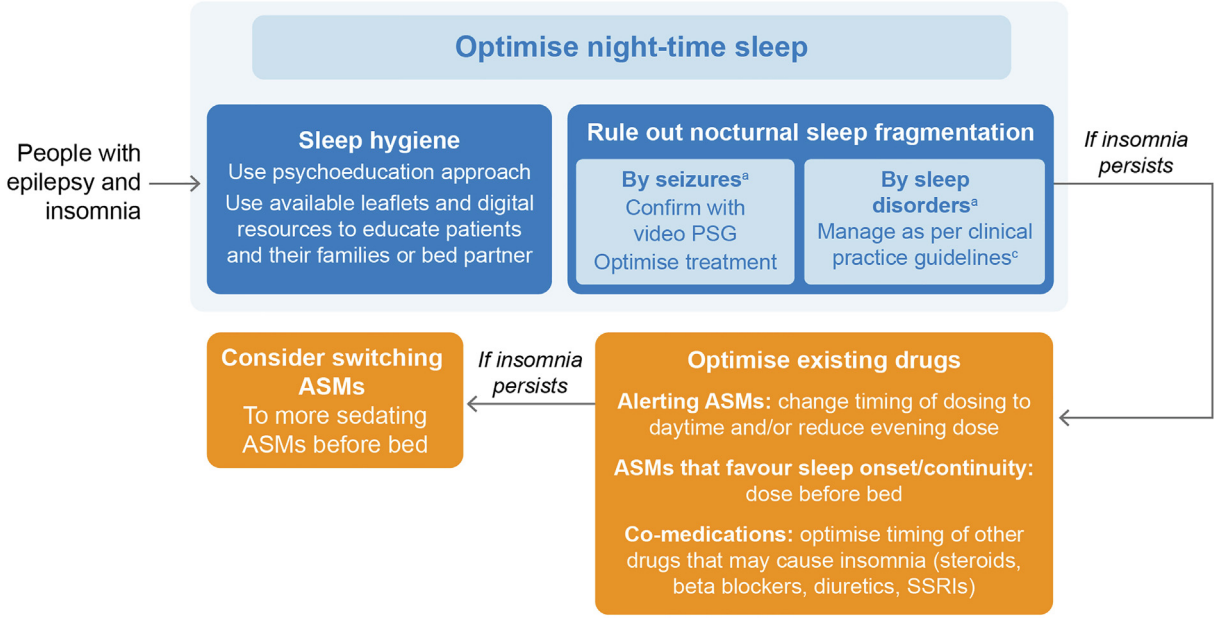

Fig. 3. Algorithm for managing poor night-time sleep. PSG, polysomnography; SSRI, selective serotonin reuptake inhibitor. [a]Refer to Nobili et al. [7] for diagnostic pathway for sleep-related epilepsies and comorbid sleep disorders.

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. 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 comedications should always be optimized in order to improve nocturnal sleep and avoid daytime sedation.

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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, Lincoln Pharma, Eisai and Fidia Pharma.

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IR has no relevant disclosures.

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