Epilepsy Currents
2021, Vol. 21(3) 204-209
© The Author(s) 2021
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/1535759721004566
journals.sagepub.com/home/epi
SAGE

Proceedings of the Sleep and Epilepsy Workshop: Section 1 Decreasing Seizures: Improving Sleep and Seizures, Themes for Future Research

Mark Quigg, MD, MSc[1,*], Carl W. Bazil, MD, PhD[2], Melanie Boly, MD, PhD[3], Erik St Louis, MD[4], Judy Liu, MD, PhD[5], Louis Ptacek, MD[6], Rama Maganti, MD[3], Frank Kalume, PhD[7], Bruce J. Gluckman, PhD[8], Jay Pathmanathan, MD, PhD[9], Milena K. Pavlova, MD[10], and Gordon F. Buchanan, MD, PhD[11]

[1] Department of Neurology, University of Virginia School of Medicine, Charlottesville, VA, USA
[2] Columbia University, New York, NY, USA
[3] Department of Neurology, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA
[4] Mayo Clinic, Rochester, MN, USA
[5] Brown University, Providence, RI, USA
[6] University of California San Francisco, CA, USA
[7] University of Washington, Seattle, WA, USA
[8] Departments of Engineering Science & Mechanics, Neurosurgery, and Biomedical Engineering, Penn State University, University Park, PA, USA
[9] University of Pennsylvania, Philadelphia, PA, USA
[10] Department of Neurology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA
[11] Department of Neurology and Iowa Neuroscience Institute, University of Iowa Carver College of Medicine, Iowa City, IA, USA
*Correspondence: Mark Quigg, Department of Neurology, University of Virginia School of Medicine, Charlottesville, VA 22903, USA; e-mail: msq6g@hscmail.mcc.virginia.edu.

Abstract

Epileptic seizures, sleep, and circadian timing share bilateral interactions, but concerted work to characterize these interactions and to leverage them to the advantage of patients with epilepsy remains in beginning stages. To further the field, a multidisciplinary group of sleep physicians, epileptologists, circadian timing experts, and others met to outline the state of the art, gaps of knowledge, and suggest ways forward in clinical, translational, and basic research. A multidisciplinary panel of experts discussed these interactions, centered on whether improvements in sleep or circadian rhythms improve decrease seizure frequency. In addition, education about sleep was lacking in among patients, their families, and physicians, and that focus on education was an extremely important "low hanging fruit" to harvest. Improvements in monitoring technology, experimental designs sensitive to the rigor required to dissect sleep versus circadian influences, and clinical trials in seizure reduction with sleep improvements were appropriate.

Keywords

seizures, sleep, circadian rhythm, SUDEP, epilepsy

Introduction to the Sleep and Epilepsy Workshop

Although sometimes both patients and physicians feel that epileptic seizures occur "out of the blue," the temporal pattern of seizure occurrence is not random. The overall chronobiological timing of seizures is the integrated sum of endogenous physiological cycles that comprise homeostatic regulation as well as perturbations arising from exogenous/environmental influences. When seizure patterns become rhythmic, the periods of

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (https://creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).

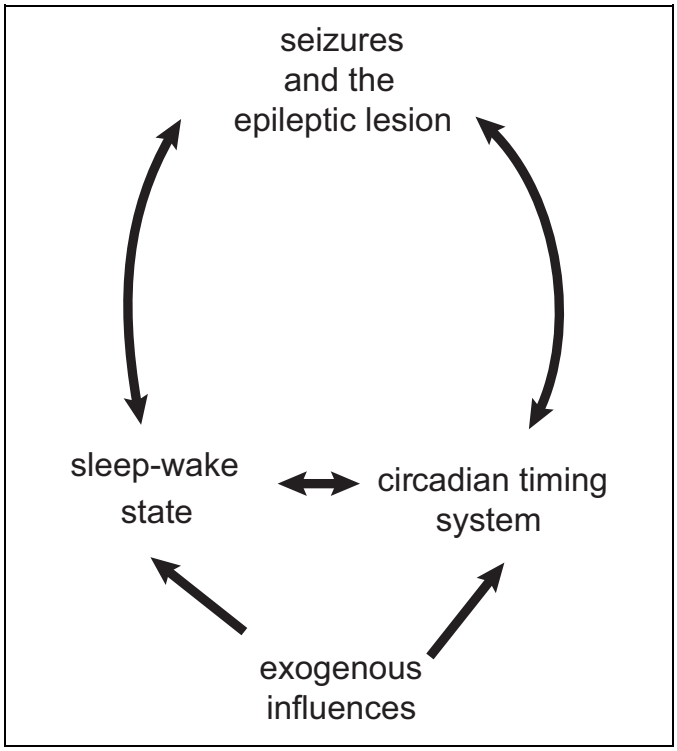

Figure 1. Sleep–wake state, the circadian timing system, and epileptic seizures maintain bilateral influences upon each other—each susceptible to exogenous modulators, to produce temporal patterns of seizure occurrence.

rhythms are traditionally organized into those with periods of less than a day (ultradian rhythms), around a day (circadian), and more than a day (infradian). Although numerous hormonal and physiological processes occur in daily patterns in mammals, the one factor they all obviously share is sleep. Medically intractable seizures occur in long-term temporal patterns that are the combined influences of biological rhythms including sleep. In turn, seizures and the underlying epileptic condition can perturb normal homeostasis and disrupt ongoing rhythms (Figure 1).

This review is the first of 3 brief reviews that tackle each of 3 areas of specific interest that the panel identified as key questions for future research. This review evaluates the interactions between sleep, circadian rhythms, and seizures, and evaluates the hypothesis that improved sleep and circadian function can improve seizure occurrence.

Effects of Sleep and Circadian Rhythms on Seizure Expression

Although not a focus area of the workshop, a brief outline of the timing of seizures is necessary to provide context. Indeed, this area has provided the preponderance of studies since the original observation of Gowers in 1885.[1] Reassuringly, advances in monitoring technology, including the most recent studies with the use of chronic implanted electrocorticography monitoring devices, have reinforced early observations. Most of these data can be concisely summarized below[2]:

1. The temporal occurrence of seizures is syndrome-dependent, with different syndromes being more or less susceptible to different endogenous factors.
2. Limbic seizures, represented by mesial temporal lobe epilepsy and its animal models, occur mainly during the day and are less precipitated by sleep than other circadian endogenous precipitants (that remain unknown).
3. Nonlimbic, cortical focal epilepsies, typified by frontal lobe epilepsy, occur mainly at night and are mainly susceptible to precipitation by non-rapid eye movement sleep (NREM) sleep.
4. Generalized epilepsies, represented by juvenile myoclonic epilepsy, tend to occur in sleep–wake transitions, especially during morning awakening.

One of the difficulties that recent studies of ambulatory, long-term, implanted electroencephalogram (EEG) have demonstrated is that the temporal occurrence of seizures is the cumulative summation of different rhythms: ultra (periods of recurrence < 24 hours), infra (>24 hours), and circadian rhythms accumulate to form a polyrhythmic, complex pattern.[3,4] Teasing apart the separate influences is challenging. For example, since sleep typically occurs during the biological "night" of an individual, it is very difficult to distinguish between the effects of sleep and the circadian system. Experimental designs that can unlink ictogenic influences attributable to sleep–wake state from the biological clock are rarely undertaken with experimental models of epilepsy[5,6] and are nearly impossible to undertake with humans; in fact, only one report has recorded human epilepsy under rigorous circadian conditions.[7] One conclusion of the workshop members was that elucidation of ictal mechanisms requires studies that can isolate various chronobiological factors.

Although currently the potential rhythmic ictogenic mechanisms remain unclear, some general observations between sleep and epilepsy have been well-described. In general, NREM sleep potentiates both the occurrence and spatial distribution of interictal epileptiform discharges (IEDs) and seizures; REM sleep inhibits both of these. More recent studies with intracranial recordings suggest that high-frequency oscillations, especially those with frequency >200 Hz, also appear more frequently during NREM sleep than other stages.[8] The mechanisms that promote IEDs or seizures during NREM sleep remain under investigation. One prevalent hypothesis is that widespread neuronal synchrony present during NREM sleep may promote entrainment of networks of neurons. A role for circadian hormonal changes, especially in melatonin, and the other rare rhythms that occur in phase among both diurnal and nocturnal mammals, have also been entertained, but evidence is contradictory.

Conversely, REM sleep can be considered an antiepileptogenic state. In a meta-analysis of 1990 focal seizures from 42 studies, only 1% of seizures occurred in REM sleep.[9] The

inhibitory effect against seizures is greater than that against interictal activity, as there were 8 to 88 times fewer focal seizures in REM sleep, but only 1.1 to 2.5 times fewer focal IEDs in REM sleep.[9] Rapid eye movement sleep also appears to inhibit seizures and IEDs in epileptic encephalopathies such as hypsarrhythmia, electrical status epilepticus in slow-wave sleep, continuous spike and waves in slow-wave sleep, and Landau-Kleffner syndrome.[10] Rapid eye movement sleep also appears to inhibit high-frequency oscillations, including ripples and fast ripples.[11] Notably, REM sleep has reportedly narrowed the electrical field of intracranial high frequency oscillations to better delineate epileptogenic cortex.[12]

Can Improvements in Sleep in Turn Reduce Seizure Frequency?

One major focus of the workshop was to evaluate current knowledge and raise an important question for patients with epilepsy (PWE): Can improving sleep improve seizure frequency?

Most epileptologists have experience with college-student aged patients who, in the midst of either work or fun (or both), experience breakthrough seizures because of sleep deprivation. Janz observed over 50 years ago that sleep deprivation and alcohol withdrawal were strong seizure precipitants.[13] Studies of military personnel and surveys of epilepsy patients noted similar findings. Obstructive sleep apnea, a known disruptor of sleep, has been associated with worsened seizure control,[14] and treatment with continuous positive airway pressure has shown to improve seizure control.[15] Insomnia, a state of hyperarousal and chronic insufficient sleep, occurs in higher rates in PWE compared to normal populations with prevalences ranging from 24% to 55%.[16-21] A survey of PWE shows that insomnia correlates strongly with seizure occurrence regardless of epilepsy syndrome.[21]

On the other hand, only one study has tried to objectively measure the effect of acute sleep deprivation on seizure occurrence in the controlled setting of an epilepsy monitoring unit (EMU)[22]; no effect of acute sleep deprivation on seizure frequency was apparent between those patients assigned to consecutive blocks of sleep deprivation and those assigned to the normal sleep. This study demonstrates some of the shortcomings that future work must overcome. The EMU may not be an appropriate setting in which to evaluate the endogenous effects of sleep–wake state on seizure occurrence. Patients in the EMU are separated from their native sleeping environment and daily activities. Delays in epileptic seizure occurrence after EMU admission compared to shorter latencies seen in those with psychogenic nonepileptic seizures attest to the "holiday effect" that some PWE experience upon admission.[23] We have noted that the sleep–wake patterns in the EMU inaccurately reflect what one would expect by time of day (Figure 2). Studies that attempt to define the potential proconvulsant effect of sleep deprivation in the EMU, therefore, need to control better for the artificial conditions of an inpatient hospital environment.

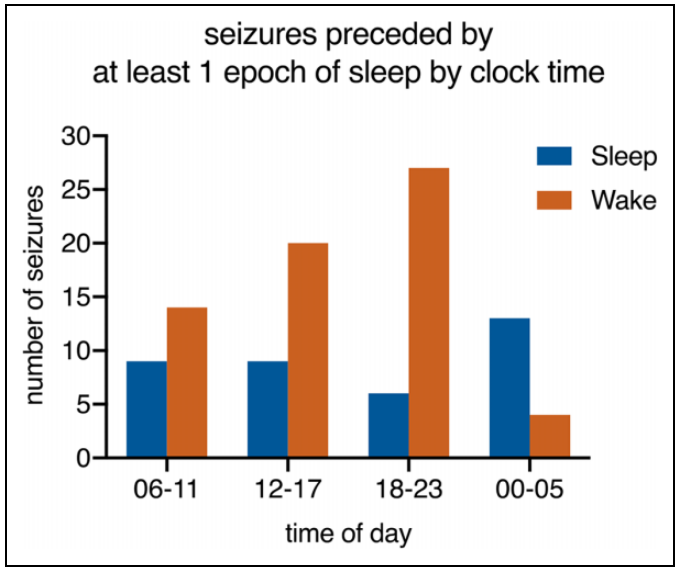

Figure 2. The temporal distribution of 101 seizures from 42 patients with medically intractable seizures according to the occurrence during sleep or wakefulness. Sleep was defined as at least one 30 second epoch of polysomnography-confirmed sleep within 5 minutes of the electrographic onset of seizures.[24] Note that seizures occurring before sleep were present at all times of day, meaning that napping, late awakening, and waking after midnight were prevalent in the noisy confines of the EMU. EMU indicates epilepsy monitoring unit.

Finally, since interactions between sleep, circadian rhythms, and seizures are intwined, seizures, by either disrupting nighttime sleep, or by leading to a prolonged sleep period postictally may cause shifts in the circadian cycle of epilepsy patients, a kind of seizure-induced "jet lag." By interrupting daily routines, seizures can promote sleep at inappropriate times of day, leading to insufficient, nonrestorative sleep for patients and for caregivers. Evidence for these hypotheses is thin.

Moving Forward

Therefore, to move forward in the area of seizure reduction, the panel made several recommendations.

Ambulatory Monitoring

The development of popular smart watches and other ambulatory devices with physiological monitoring capabilities may transform the evaluation of sleep. For example, the plethysmographic detection of pulse in the Apple smart watch has already emerged in the lay press as a "life saver" in cases of cardiac arrhythmia. The medical use of wearable technology is a rapidly evolving subject.[25] A recent comparison of a variety of trackers found that there remained a large variability among tracker brands compared to sleep diary notations. Some trackers, however, were more accurate in reflecting sleep diaries than older "medical grade" actigraphs.[26] Similar variability among trackers has been evaluated in comparison with home

polysomnography in normal adults[27] and with standard polysomnography in patients with obstructive sleep apnea.[28]

Electroencephalogram is in a similar race to provide reliable, long-term ambulatory monitoring. Several groups have taken advantage of the detection capabilities of the responsive neural stimulator (RNS) in its role as a long-term recorder of epileptic events and seizure detections.[3,4] The RNS may serve as a proof of concept for an ambulatory "seizure diary"[29] that improves upon the inaccuracy of the "gold-standard" of the self-reported seizure diary.[30,31] Several companies are developing subdermal, supracalvarial EEG devices that could serve as a golden compromise between accuracy, tolerance, and invasiveness for long-term monitoring of seizures.

The advantages of the host of ambulatory devices are clear. Reliable monitoring can objectively elucidate seizure patterns while confirming the timing and severity of seizures in individual patients monitored for long period of time. Human studies of both pathophysiology and treatment can benefit accordingly by lowering cost, enabling monitoring in both controlled and native environments, and allowing expanded pools of data. And, of course, technological advances in physiological monitoring are not confined to human epilepsy. Experimental animal models can benefit from similar reductions in equipment size, invasiveness, and cost. The group concluded that ambulatory devices that can score sleep and detect and time-stamp seizures would be a fundamental advance in the field.

Treatment Trials

The above advances in monitoring can go hand-in-hand with a new emphasis on basic science studies on mechanisms by which sleep dysregulation promotes seizure occurrence. Translational and clinical research should concentrate on treatments to improve sleep, observe resultant changes in seizure control (or a surrogate marker), and measure the mediating effects of improved sleep upon seizure control. Such experiments offer a kind of "two-for-the-price-of-one" bargain. Since improved sleep has salutatory effects on cognition, attention, and mood, patients may benefit not only from any reductions in seizures but in the result of improved sleep as a beneficial "side-effect" of treatment. Such dual benefits are commonly recognized already in the use of topiramate in PWE with comorbidities of chronic headache[32] or lamotrigine in mood disorders.[33] Patients with epilepsy with a comorbid sleep disorder stand to gain doubly.

Monitoring Environment

There is a reason only one study to date has monitored PWE under environmental conditions that can rigorously separate circadian from sleep effects on seizure occurrence[7]; it is expensive and difficult. Wever and Aschoff's landmark studies of circadian timing in humans were performed in underground bunkers for long-term temporal isolation.[34] This isn't to say that these conditions are required for all potential experiments, but investigators and their readers should keep in mind that when a study purports to be a study of "circadian" phenomena, what the vast majority of designs are measuring are 24-hour distributions of phenomena of both exogenous and endogenous control. Entraining influences that are external to the animal, such as light–dark exposure, mealtimes, stimulation or exercise, anticonvulsant administration, or other habitual, daily activities or stressors could serve to constrain seizure expression in a diurnal, exogenously mediated pattern. On the other hand, endogenous rhythms, such as circadian rhythms of electrical activity originating in the brain's clock—the suprachiasmatic nucleus—or the circadian fluctuations of hormones may influence endogenous, circadian timing of seizures.

The rigor required to dissect the influences of sleep from those of circadian rhythms is outlined below. Some experiments, as mentioned above, use long-term chronic isolation from external time cues. A more practical protocol is "constant routine." In these experiments, the tested individual is kept continuously awake in otherwise constant conditions, and thus any circadian variation observed is due to endogenous circadian effects rather than state of sleep versus wake. However, "constant routine" is not appropriate for evaluating seizures or any other measures in PWE since sleep deprivation may be a key component in seizure exacerbation.

Methods that do not mandate sleep deprivation but still allow separating the effects of circadian rhythms for sleep/wake state in humans include "forced desynchrony." The best way to describe this is to imagine being on a different planet where the length of the day is different from 24 hours. The tested individual is scheduled to sleep periodically in that planet's day—periods range 20 minutes[35] to 42 hours.[36] The individual, still "living on Earth" and tied to his internal 24 circadian clock, now can have parameters measured according to the non-24 hour sleep cycle against an independent 24-hour circadian cycle. A protocol of 4 days duration, which was tolerated in a pilot phase without any adverse consequences for the participating individuals with epilepsy, has been successfully used to study circadian distribution of epileptiform discharges.[7] However, the expense and heavy resource utilization of such protocols make them challenging. Furthermore, it requires smooth interaction between the epileptologists and circadian physiologists for implementation. Having a well-established multidisciplinary team may allow a more focused approach in the design and more efficient use of resources. The panel encouraged greater education of basic principles of chronobiology to the epilepsy community. Experiments with controlled monitoring environments could not only aid in evaluating the salutary effects of sleep on seizure control but could evaluate the potential deleterious effects that seizures have on the synchronization between circadian rhythms and sleep. Effects of inappropriate or insufficient sleep will be important in improving overall quality of life in PWE and their caregivers.

Summary

In 2 subsequent articles, we will review the background and recommendations for future development in the workshop's other major areas of the interactions of sleep, circadian regulation, and epilepsy. Our overall goal is to encourage rigorous research in an area that may profoundly improve the lives of PWE and their families. The Sleep and Epilepsy Workgroup hopes to become a lasting presence to encourage research and education in this exciting area.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Funding for the Sleep Epilepsy Workshop was provided by the Band Foundation.

ORCID iDs

Judy Liu https://orcid.org/0000-0001-9272-9517
Rama Maganti https://orcid.org/0000-0001-5472-1645
Bruce J. Gluckman https://orcid.org/0000-0001-7695-2225
Gordon F. Buchanan https://orcid.org/0000-0003-2371-4455

References

1. Gowers W.Course of epilepsy. In: Gowers W, ed. *Epilepsy and Other Chronic Convulsive Diseases: Their Causes, Symptoms and Treatment*. William Wood; 1885;157-164.
2. Quigg M. Circadian rhythms: interactions with seizures and epilepsy. *Epilepsy Res*. 2000;42(1):43-55.
3. Spencer DC, Sun FT, Brown SN, et al. Circadian and ultradian patterns of epileptiform discharges differ by seizure-onset location during long-term ambulatory intracranial monitoring. *Epilepsia*. 2016;57(9):1495-1502.
4. Baud MO, Kleen JK, Mirro EA, et al. Multi-day rhythms modulate seizure risk in epilepsy. *Nat Commun*. 2018;9(1):88.
5. Quigg M, Straume M, Menaker M, Bertram EH. Temporal distribution of partial seizures: comparison of an animal model with human partial epilepsy. *Ann Neurology*. 1998;43(6):748-755.
6. Wallace E, Wright S, Schoenike B, Roopra A, Rho JM, Maganti RK. Altered circadian rhythms and oscillation of clock genes and Sirtuin 1 in a model of sudden unexpected death in epilepsy. *Epilepsia*. 2018;59(8):1527-1539.
7. Pavlova MK, Shea SA, Scheer FA, Bromfield EB. Is there a circadian variation of epileptiform abnormalities in idiopathic generalized epilepsy? *Epilepsy Behav*. 2009;16(3):461-467.
8. Frauscher B, Bartolomei F, Kobayashi K, et al. High-frequency oscillations: the state of clinical research. *Epilepsia*. 2017;58(8):1316-1329.
9. Ng M, Pavlova M. Why are seizures rare in rapid eye movement sleep? Review of the frequency of seizures in different sleep stages. *Epilepsy Res Treat*. 2013;2013:932790.
10. Kohyama J, Shimohira M, Tanuma N, Hasegawa T, Iwakawa Y. ACTH activates rapid eye movement-related phasic inhibition during REM sleep in patients with infantile spasms. *Acta Neurol Scand*. 2000;101(3):145-152.
11. Im HJ, Park SH, Baek SH, et al. Associations of impaired sleep quality, insomnia, and sleepiness with epilepsy: a questionnaire-based case-control study. *Epilepsy Behav*. 2016;57(Pt A):55-59.
12. Lieb JP, Joseph JP, Engel J Jr, Walker J, Crandall PH. Sleep state and seizure foci related to depth spike activity in patients with temporal lobe epilepsy. *Electroencephalogr Clin Neurophysiol*. 1980;49(5-6):538-557.
13. Janz D. The grand mal epilepsies and the sleeping-waking cycle. *Epilepsia*, 1962;3:69-109.
14. Devinsky O, Ehrenberg B, Barthlen G, Abramson H, Luciano D. Epilepsy and sleep apnea syndrome. *Neurology*. 1994;44(11):2060-2064.
15. Malow BA, Weatherwax KJ, Chervin RD, et al. Identification and treatment of obstructive sleep apnea in adults and children with epilepsy: a prospective pilot study. *Sleep Med* 2003;4(6):509-515.
16. Xu X, Brandenburg N, McDermott A, Bazil CW. Sleep disturbances reported by refractory partial-onset epilepsy patients receiving polytherapy. *Epilepsia*. 2006;47(7):1176-1183.
17. Malow BA, Levy K, Maturen K, Bowes R. Obstructive sleep apnea is common in medically refractory epilepsy patients. *Neurology*. 2000;55(7):1002-1007.
18. 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(6):836-840.
19. Vendrame M, Yang B, Jackson S, Auerbach SH. Insomnia and epilepsy: a questionnaire-based study. *J Clin Sleep Med*. 2013;9(2):141-146.
20. de Weerd A, de Haas S, Otte A, et al. Subjective sleep disturbance in patients with partial epilepsy: a questionnaire-based study on prevalence and impact on quality of life. *Epilepsia*. 2004;45(11):1397-1404.
21. Quigg M, Gharai S, Ruland J, et al. Insomnia in epilepsy is associated with continuing seizures and worse quality of life. *Epilepsy Res*. 2016;122:91-96.
22. Malow B, Pasaro E, Hall J, et al. Sleep deprivation does not increase seizure frequency during long term monitoring [abstract]. *Epilepsia*. 1999;40:40.
23. Perrin MW, Sahoo SK, Goodkin HP. Latency to first psychogenic nonepileptic seizure upon admission to inpatient EEG monitoring: evidence for semiological differences. *Epilepsy Behav*. 2010;19(1):32-35.
24. Schomer AC, Lynch M, Leonardo J, et al. *Personal Communication*. American Psychological Association; 2020.
25. Carpenter AC, Frontera A. Smart-watches: a potential challenger to the implantable loop recorder? *EP Europace*. 2016;18(6):791-793.
26. Lee JE, Lee DH, Oh TJ, et al. Clinical feasibility of monitoring resting heart rate using a wearable activity tracker in patients with thyrotoxicosis: prospective longitudinal observational study. *JMIR Mhealth Uhealth*. 2018;6(7):e159.
27. Gruwez A, Libert W, Ameye L, Bruyneel M. Reliability of commercially available sleep and activity trackers with manual

switch-to-sleep mode activation in free-living healthy individuals. *Int J Med Inform*. 2017;102:87-92.

28. Gruwez A, Bruyneel AV, Bruyneel M. The validity of two commercially-available sleep trackers and actigraphy for assessment of sleep parameters in obstructive sleep apnea patients. *PLoS One*. 2019;14(1):e0210569.
29. Quigg M, Skarpaas TL, Spencer DC, Fountain NB, Jarosiewicz B, Morrell MJ. Electrocorticographic events from long-term ambulatory brain recordings can potentially supplement seizure diaries. *Epilepsy Res*. 2020;161:e106302.
30. Fisher RS, Blum DE, DiVentura B, et al. Seizure diaries for clinical research and practice: limitations and future prospects. *Epilepsy Behav*. 2012;24(3):304-310.
31. Quigg M.Monitoring seizure frequency and severity in outpatients. In: Schachter S, ed. *Evidence-Based Management of Epilepsy*. TFM; 2011;21-31.
32. Spritzer SD, Bravo TP, Drazkowski JF. Topiramate for treatment in patients with migraine and epilepsy. *Headache*. 2016;56(6): 1081-1085.
33. Ettinger AB, Kustra RP, Hammer AE. Effect of lamotrigine on depressive symptoms in adult patients with epilepsy. *Epilepsy Behav*. 2007;10(1):148-154.
34. Wirz-Justice A, Daan S, Folkard S, Lewy A, Lund R, Zulley J.Rutger Wever: an appreciation. *J Biol Rhythms*. 2005;20(6):554-555.
35. Lavie P.Ultrashort sleep-waking schedule. III. "Gates" and "Forbidden zones" for sleep. *Electroencephalogr Clin Neurophysiol*. 1986;63(5):414-425.
36. Bermudez EB, Klerman EB, Czeisler CA, Cohen DA, Wyatt JK, Phillips AJ. Prediction of vigilant attention and cognitive performance using self-reported alertness, circadian phase, hours since awakening, and accumulated sleep loss. *PLoS One*. 2016;11(3): e0151770.