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Neurostimulation and sleep in patients with epilepsy—English version

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| Abstract |

Background: Chronic sleep disturbance may affect seizure frequency and efficacy of treatment in epilepsy patients. Vagus nerve stimulation (VNS) and deep brain stimulation (DBS) can both induce sleep disturbance as a side effect.
Aim: The goal of this review is to provide information and clinical advice about potential interactions between DBS at the anterior nucleus of the thalamus (ANT) and sleep as well as between VNS and sleep.
Materials and methods: We provide an up-to-date overview of the currently available literature, giving insights for diagnostics and therapy based on clinical studies, and experience in two epilepsy centers with longitudinal cohorts of patients under chronic neurostimulation.
Results: In patients with chronic ANT-DBS and VNS, stimulation-correlated, probably dose-dependent sleep disturbances have been reported in several studies. The reason for this is assumed to be an accidental co-stimulation of the ascending reticular arousal system in the case of DBS, and an indirect effect via induction of sleep-related breathing disorders in the case of VNS. Furthermore, VNS might also influence sleep through modulation of noradrenergic and dopaminergic, arousal-inducing systems in the pons and midbrain. Reduction of stimulation amplitudes, changes in stimulation parameters, and localization of the active stimulation zone are discussed as treatment strategies in DBS. In the case of VNS-induced sleep disturbance, a nocturnal reduction of stimulation (bilevel therapy) can be offered.
Conclusion: As data are currently still sparse, it seems important to optimize treatment regimens for VNS and DBS in order not to antagonize their potential anticonvulsant effects by inducing sleep fragmentation.

Keywords
Sleep disturbance · Sleep apnea · Arousal · Deep brain stimulation · Vagus nerve stimulation

Introduction

Sleep is important, not only for well-being and quality of life but also for daytime vigilance, affect stability, storage of memory content, and for the maintenance of vital functions. Chronic sleep fragmentation leads to daytime fatigue, reduced performance, and neuropsychological deficits as well as to secondary internal diseases such as arterial hypertension, type 2 diabetes, and increased cardio- and cerebrovascular risks.

In epilepsy patients, chronic sleep fragmentation also has the potential to initiate a vicious somnological/epileptological cycle of sleep fragmentation, arousal induction, sleep deprivation, provocation of sleep deprivation-induced seizures from wakefulness, and arousal-induced seizures from sleep, which in turn result in worsening of sleep fragmentation (◘ Fig. 1).

Chronic sleep fragmentation of this kind can lead to sleep disorders such as obstructive sleep apnea (a comorbidity in approximately 30% of all patients with difficult-to-treat epilepsy studied in epilepsy mon-
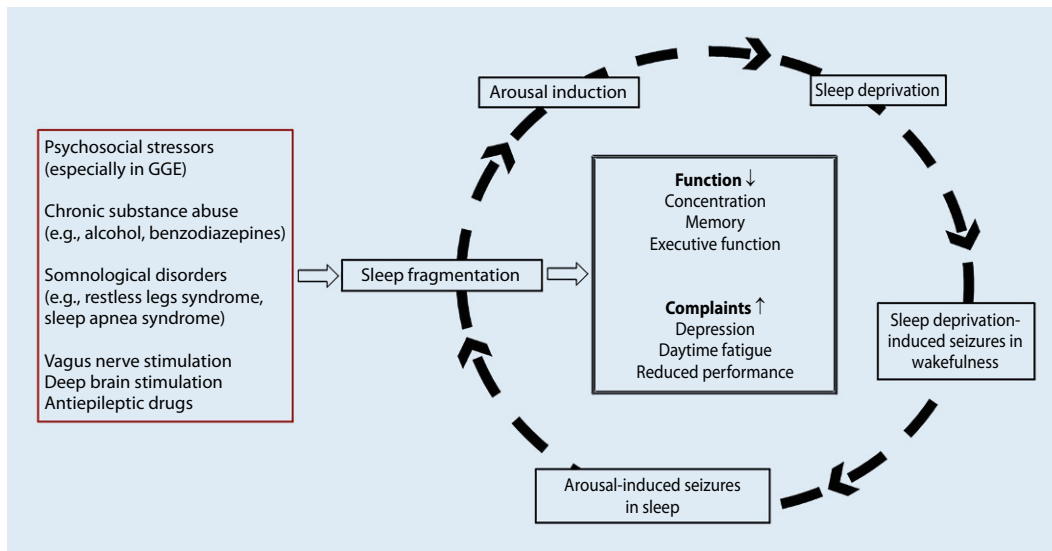
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Fig. 1 ◄ Somnological/epileptological vicious cycle showing potential triggers of sleep fragmentation (*left, red box*), the progressively worsening somnological and epileptological parameters (*circle*), and the resulting functional impairments and symptoms. *GGE* genetic generalized epilepsy. (From [39])

itoring [30]), restless legs syndrome, and insomnia in epilepsy patients, resulting in a worsening of the seizure situation and even treatment refractoriness. This has been clearly demonstrated for untreated sleep apnea, for example, with induced arousal being the major pathophysiological factor in the individual apnea event [4].

However, anticonvulsant therapies can also exert a similar proconvulsive effect if they lead to sleep disturbances as an adverse side effect. This may be the case with seizure-suppressing drugs with vigilance-increasing potential administered in the evening (such as high-dose lamotrigine) or with the two methods of neurostimulation for epilepsy approved in Germany. Sleep-disturbing effects have been described for deep brain stimulation (DBS) at the anterior nucleus of the thalamus (ANT) as well as for vagus nerve stimulation (VNS). To ensure that these do not antagonize the anticonvulsant effect of neurostimulation—so urgently needed for the respective patients with difficult-to-treat epilepsy—it is important to know not only the potential interaction between DBS or VNS and sleep but also the possibilities to mitigate this therapeutic dilemma. This article provides an overview of this topic.

Deep brain stimulation in the ANT and sleep

Deep brain stimulation is an effective second-line therapy for patients with phar-macoresistant focal epilepsy [10, 26]. The ANT is currently the most commonly used target in epilepsy patients since this structure plays an important role in the propagation and synchronization of ictal activity. In particular, as a connecting structure between the two hemispheres, the ANT is involved in the spread of epileptic activity to the contralateral hemisphere and thus in the maintenance of bilateral epileptic seizures. Accordingly, current disease models in epilepsy with focal and bilateral tonic-clonic seizures suggest failure of the basal ganglia as an inhibitory system and overactivity in the thalamus. Thus, according to this model, neuronal inhibition of the ANT by high-frequency DBS may inhibit seizure propagation and raise the seizure threshold [13, 36, 38]. Studies on the efficacy of ANT-DBS in status epilepticus support this hypothesis and show that thalamocortical epileptic networks can also be acutely inhibited by high-frequency stimulation [16].

In addition to its effect on seizure-producing networks in epilepsy, the ANT also plays an important role as a connecting structure between the cortex and limbic structures. Within this network (neuroanatomically defined as the *Papez circuit*), the hippocampus projects to the ANT via the fornix and mamillary bodies. Further projections from the ANT to the cingulate and via the cingulate gyrus to the parahippocampal cortex are then connected back to the hippocampus [8]. Accordingly, possible psychiatric side ef-fects of chronic ANT-DBS include depression and deterioration of memory function [9, 17, 26]. In addition, however, the ANT is also associated with the ascending reticular activating system (ARAS), a key structure for the control of vigilance [8]. Of particular importance in this context is that the reticular thalamic nucleus, as an important sleep-promoting structure, lies in direct contact with the superior ANT and is connected to it via inhibitory interneurons [32]. Thus, stimulation of the anterior thalamus and its associated interaction with sleep regulatory networks could affect both sleep architecture and sleep microstructure (i.e., sleep EEG characteristics). Surprisingly, in the pivotal studies of ANT-DBS in epilepsy, changes in sleep–wake behavior under DBS were not observed or not systematically recorded [9, 27]. However, clinical application of ANT-DBS in epilepsy patients showed evidence of a relevant interaction between thalamic DBS and physiological sleep regulation.

Deep brain stimulation and sleep architecture

Voges et al. [35] were the first to investigate the effect of cyclic (1 min ON/5 min OFF) ANT-DBS on sleep in a cohort of nine patients with epilepsy. In this study, paroxysmal interruptions of deep sleep (arousals) occurred on average about three times more frequently in the ON stimulation phases compared with OFF stimulation. Although patients did not report sub-

jective sleep problems, polysomnographic studies showed DBS-induced sleep fragmentation in the majority of these patients: At treatment voltages of 5 V, an average of 43% (17–78%) of all DBS stimulations resulted in simultaneous electrographic arousals or clinical awakening in the patients. Overall, this woke patients four times (1.7–7.8 times) per hour during active DBS. Finally, the reduction in nighttime treatment voltage led to the reduction of intermittent sleep disturbance in a dose-dependent manner and, consecutively, affective and memory disturbances. Thus, it can be inferred that sleep fragmentation is causally directly related to cyclic high-frequency DBS. This hypothesis is supported by the observation that "bilevel" therapy (i.e., reduction of stimulation amplitude selectively at night) in this group of patients produced a significant decrease in sleep disturbance with, if anything, an improved effect on seizure suppression. Meanwhile, depending on the manufacturer, stimulation generators are offered with corresponding programmability in order to enable users to perform this bilevel treatment in the case of relevant symptoms.

Various mechanisms can be considered as the cause of this stimulation-dependent sleep fragmentation. In the Hamburg cohort [35], the inferior portion of the ANT or the mammillothalamic tract (MMT) was targeted in an extraventricular approach. The resulting "tract stimulation" could potentially exert an activating effect through interaction with the reticular system (ARAS), e.g., via retrograde axonal stimulation [19].

On the other hand, another relevant influence on sleep architecture may be the stimulation mode, since arousals regularly occur at stimulation onset. Centers that, in contrast to Voges et al. [18], use continuous ANT-DBS as the default DBS mode rarely report sleep–wake rhythm disturbances in their collectives. Further studies will need to show in the course whether the target or the stimulation mode is primarily responsible for the impaired sleep regulation.

Deep brain stimulation and sleep microstructure

However, in addition to the regulation of sleep stages, the thalamus is also of particular interest for the physiology of sleep EEG (sleep microstructure; [32]). The classic seminal work of Steriade et al. [20, 31] showed that the thalamus plays a crucial role in the generation and regulation of cortical sleep EEG elements such as spindles and delta waves. In this context, various animal models have shown that delta waves are generated mainly in the cortex and appear in the thalamus with a small time delay, whereas higher-frequency spindle activity is generated mainly in the thalamus and projects to the cortex [6]. Moreover, a relevant reciprocal interaction between thalamic delta activity and spindle activity is observed: While positive delta "down states" in the thalamus suppress spindle activity, the delta "up state" synchronizes spindle activity. Functionally, this control is based on thalamic burst-firing episodes, which are modulated by inhibitory input from the thalamic reticular nucleus.

A unique opportunity is now provided by ANT-DBS to test these hypotheses in humans by measuring intracranial field potentials in the thalamus (e.g., by postoperative lead-out electrodes). Studies with intracranial leads in humans support the model of intense thalamocortical interaction during deep sleep. For example, in a descriptive study with three epilepsy patients and leads from the anterior thalamus, it was shown that sleep spindles and delta activity occur coherently in the anterior thalamus and ipsilateral cortex with a slight temporal shift [33]. Another study also shows that thalamic sleep spindles are detectable immediately *before* the corresponding cortical elements, whereas thalamic delta waves occur in a slightly delayed manner [29], thereby confirming that cortical non-REM down states can induce thalamic down states in the sense of a cortico-subcortical interaction [33]. A recent and somewhat broader-based study confirmed this interaction in a larger cohort: Thalamic delta activity follows cortically leading delta activity in different thalamic DBS target areas [34].

What happens to these sleep elements when inhibitory high-frequency stimulation is applied therapeutically in the anterior thalamus? There are no prospective studies on this subject at present. A currently ongoing retrospective analysis [2] shows that anterior thalamic stimulation in the superior part of the ANT leads to an accentuation of cortical delta activity. This implies that, in addition to sleep architecture [35], the regulatory networks of sleep elements may also be affected by subcortical stimulation. Regarding the mechanisms, the cause of this effect remains unclear; direct anterior thalamic inhibitory effects are possible, but indirect efferent stimulation in the area of the reticular nucleus of the thalamus could also be causative.

In summary, DBS in the anterior thalamus provides the possibility to measure local field potentials either by conducted microelectrodes or at the implanted device. This yields important evidence for sleep regulation, especially of non-REM sleep and the generation of sleep microelements such as sleep spindles and delta sleep. In addition, evidence is also emerging that cyclic DBS in particular influences sleep architecture through anterior thalamic stimulation. The extent to which the target, stimulation mode, and treatment response are related to these effects and whether relevant biomarkers of treatment response can also be derived from them remains to be investigated in further prospective studies.

VNS and sleep

Vagus nerve stimulation is an additive therapy for the treatment of refractory epilepsy, approved in Europe since 1994 and in the United States since 1997.

The VNS Therapy® system (LivaNova PLC, Houston, TX, USA) consists of an implanted, battery-powered pulse generator that delivers, via an implanted electrode, electrical signals to the vagus nerve at regular intervals ("OFF time") of, e.g., 3 or 5 min with predefined stimulation ON times of, e.g., 30 s—around the clock, every day and every night. In addition, by means of a magnet, the patient or caregiver can externally trigger an additional, usually stronger "on-demand stimulation" in

the VNS generator with the aim of thereby interrupting an already ongoing seizure. Finally, the newer VNS generator models available since 2013 and 2017 (Model 106 AspireSR® and Model 1000 Sentiva®, respectively, LivaNova PLC) offer—in addition to the aforementioned basic functions—the possibility of "responsive" autostimulation: These generators can detect heart rate. If there is now a rapid increase in heart rate above a predefined threshold, this is interpreted by the generator as "ictal tachycardia," which leads via a closed-loop system to the triggering of additional, so-called autostimulation. This is sometimes preset to be stronger and usually last longer (e.g., 60 s) than the basic stimulation pulse and—as with triggering by means of a magnet—has the goal of interrupting an already ongoing seizure. All settings of the VNS stimulation parameters ("output current" [mA], signal frequency [Hz], pulse width [μs], signal ON and OFF times) are individually titrated and repeatedly checked or modified during the course of therapy to achieve the best balance between anticonvulsive effect and undesirable side effects.

Sleep-related breathing disorders under VNS

Common side effects described early on include stimulus-dependent hoarseness, voice disturbance, and coughing [21]. In addition, effects on sleep or daytime wakefulness were also described early on: A positive effect on objective sleep parameters was shown for VNS in epilepsy in a study of 15 children [12]. In two studies of adults, prolonged sleep latency, as a marker for improved daytime vigilance, was found after 3 and 6 months, respectively, in patients with no more than 1.5 mA VNS stimulation current in multiple sleep latency tests, independent of anticonvulsant response. However, at higher current levels (> 1.5 mA), this effect appeared to be reversed [11, 22]. As a plausible explanation for a reduction in sleep quality especially under high VNS current levels, it was shown retrospectively that VNS stimulation induces sleep-related respiratory disturbances [14, 23, 25, 28]. This observation was confirmed in two comparative studies: In the first [23], polysomnogra-

phies were performed for 16 patients before and after initiation of VNS therapy, with recording of an apnea–hypopnea index (AHI) > 5/h in one patient before VNS and in five patients under VNS, with AHI values between 6 and 11/h, in each case indicating a mild sleep apnea syndrome (SAS). A later study with a similar design [28] pointed in the same direction: Whereas SAS was found in only two of the 18 patients studied before VNS therapy, VNS caused a worsening in AHI in one of these two (but an improvement in the other) and new-onset sleep apnea in four of the 18 patients. The cause of apnea induction by VNS seems to be accidental costimulation of the lateral branches of the vagus nerve, the recurrent nerve, and the superior laryngeal nerve, which leads to a toning of their motor supply areas in the pharynx and on the left vocal cord and thus to—laryngoscopically proven—restriction of the airway during VNS-ON phases [37]. Attempts to counteract these VNS-induced apneas with continuous positive airway pressure (CPAP) therapy proved ineffective in most patients [24]; in one patient with comorbidity of epilepsy and obstructive sleep apnea syndrome (OSAS), VNS had to be deactivated to enable adequate CPAP titration [7]. The reason for the ineffectiveness of CPAP on VNS apnea is likely due to the different pathophysiologies: Obstructive SAS is due to wall weakness of a hypotonic soft palate that cannot withstand the negative pressure during the inspiratory phase and collapses. In VNS-induced apnea, however, as described above, electrical stimulation leads to toning and constriction in the soft palate and thus to upper airway restriction, which cannot be prevented even by CPAP.

This problem is of clinical relevance: In around one tenth of the 225 patients who underwent implantation in Hamburg and then treated at our outpatient clinic, we have the clinical impression that with VNS an SAS has either newly developed or a pre-existing SAS has been relevantly worsened, as shown in the example in ◘ **Fig. 2** of one of our patients. In her case, we were able to objectively identify the induction of relevant apneas in our sleep laboratory, which is affiliated to the "epilepsy monitoring unit": We extended

the usual polysomnography with an additional electrode at the neck, placing it directly over the point at which the VNS electrode cable is attached to the vagus nerve. This facilitated visualization of the VNS stimuli, enabling the correlation between VNS stimuli and the occurrence of sleep-related breathing disorders.

The induction of sleep-related respiratory disturbances has been increasingly perceived as a numerically and substantively relevant problem in the past 7 years, possibly due to the fact that we have been increasingly working with the autostimulation described above, i.e., the automatic activation of a 60-s additional impulse in the VNS generator in the event of an abrupt increase in heart rate. Cardiac accelerations of this kind occur during sleep not only in the context of ictal tachycardia, but also, for example, by arousals or autonomic alarm reactions in sleep-related respiratory disorders. Thus, a chain of events consisting of apnea—heart rate increase—VNS autostimulation (with a duration of 60 s) can then lead to a further now longer and stronger apnea, which, if this happens frequently, can drastically worsen possibly pre-existing sleep apnea (for incidence, see above), with the aforementioned consequences in the epileptological–somnological vicious cycle (see ◘ **Fig. 1**).

Sleep apnea is a disease-aggravating risk factor in patients with epilepsy, as shown, e.g., in a polysomnographic study of older epilepsy patients: The subgroups with poor vs. good response to antiseizure medication differed mainly with respect to the presence or degree of comorbid SAS [4].

Therefore, if on the one hand VNS can trigger or worsen sleep apnea and on the other hand sleep apnea is an epilepsy-worsening risk factor, the physician (and patient!) may find themselves facing a therapeutic dilemma: The goal of VNS therapy in difficult-to-treat epilepsy is to improve the seizure situation and not to worsen it.

Arousals and increased vigilance under VNS

Induction of respiratory disturbances is not the only mechanism by which VNS therapy can lead to sleep fragmentation. In
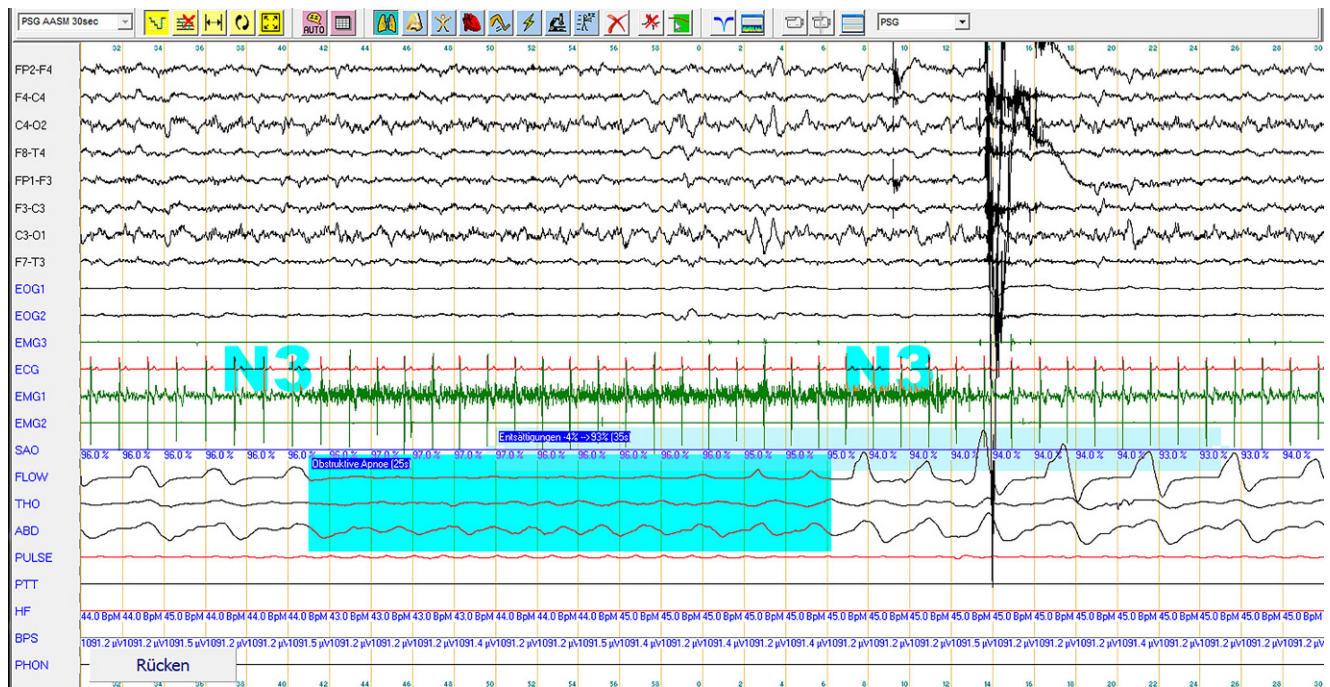
Fig. 2 ▲ Recording of vagus nerve stimulation (VNS)-induced apnea in extended polysomnography. A 30-s polysomnography in non-rapid eye movement sleep with an additional electrode over the attachment point of the VNS stimulation electrode on the vagus nerve (EMG channel 1, *green*) to visualize the activity of the VNS. With the onset of the stimulation phase, apnea is evident at the cessation of nasal flow with reduced and opposing thoracic/abdominal excursions. At the end of VNS stimulation, breathing resumes. With the usual delay of 10–30 s, consecutive oxygen desaturation occurs. During the night studied, and under a VNS output current of 1.75 mA, this female patient was found to have 22 times more respiratory disturbances per minute of sleep in VNS-ON phases than in VNS-OFF phases; 45% of all VNS-ON phases were accompanied by respiratory disturbances

recent years, we have been able to objectively identify an increased occurrence of arousals in VNS-ON in some patients in polysomnographic monitoring diagnostics without prior VNS-related respiratory disturbance.

It is possible that here VNS stimulation has a direct cerebral arousal effect. The vagus nerve has direct projections to the reticular formation, via the nucleus of the solitary tract to the ventrolateral preoptic thalamus and via the parabrachial nucleus to the locus coeruleus and dorsal raphe nuclei and, thus, to regions functionally related to mood and sleep–wake regulation. The VNS could trigger direct stimulation of noradrenergic and dopaminergic systems in the pons and midbrain, resulting in increases in arousal and vigilance, respectively [12].

Supporting evidence for neuroanatomical hypotheses of this kind was found in animal models using behavioral observation, invasive EEG [15], multiunit recordings, calcium imaging [5], immunohistochemical studies [1], and functional MRI [3], with signs of stimulation-correlated VNS activation of the locus coeruleus, cholinergic and noradrenergic subcortical efferents, dopaminergic substantia nigra, and dopaminergic ventral tegmentum.

Such arousal induction by VNS could explain the VNS-associated movement times during sleep described by Hallböök in 2005 in a group of 15 children, as well as the prolongation of multiple daytime sleep latencies in patients with VNS at an output current < 1.5 mA measured by Malow in 2001 [12, 22].

During the day, an arousal effect by VNS (or equally by DBS) could be highly positive for patients with epilepsy: Vigilance could improve, psychomotor tempo could accelerate, with supportive effects on cognitive skills. It could possibly also shorten postictal loss of consciousness or somnolence, potentially reducing the risk of sudden unexpected death in epilepsy. These are all effects that have already been described in the literature based on empirical observations of patients undergoing VNS therapy, and for which an explanation could be found here.

However, if such an induction of arousal and vigilance occurs during the night, this has negative consequences for sleep continuity and quality. Sleep fragmentation thus induced can—as can the induction of SAS—lead to the somnological–epileptological vicious cycle described above and thus, as consequence, to an exacerbation of seizures and worsening of vigilance and quality of life: The desired effect of VNS would thus be antagonized. Therefore, we find ourselves in the same therapeutic dilemma as we have already found in patients with ANT-DBS (see section on ANT-DBS [35]).

Management of VNS-induced sleep disorders

As a solution, our Hamburg center started to perform a day/night bilevel therapy for patients with VNS-induced sleep disorders in 2016, similar to the procedure for our patients with sleep fragmentation under

DBS. A therapy concept of this kind is facilitated and made feasible by a generator model that has been available since 2017 and which allows for the programming of two different therapy programs: With output current, ON-time, OFF-time, pulse width and signal frequency, all parameters can now be set specifically for the time of day; the times at which the generator automatically switches between the day and night program are programmed according to the patient's lifestyle.

During the day, we employ the commonly used parameters with, e.g., output current of 1.5–1.75 mA, pulse width of 250 μs, frequency of 20 Hz, and 30 s ON-time for the normal mode stimulus and 60 s ON-time for autostimulation. At bedtime, the program switches to a weaker "night program" with reduced "output current", e.g., 0.625 mA, 0.75, or 1 mA for "normal mode" and autostimulation, and only 30 s ON-time for autostimulation. This information is based on our own clinical experience at our center; multicenter studies or recommendations are not yet available. Under such a day/night bilevel therapy, we often see good clinical effects on mood, daytime vigilance, and also with regard to better seizure control. A worsening of the seizure situation after switching from standard VNS therapy to (at night more weakly dosed) bilevel therapy has not occurred in any of our patients to date.

In patients with VNS generator models without the possibility of day–night conversion, VNS-induced sleep disturbances could be mitigated by lowering the general output current to values < 1.5 mA or/and by reducing the ON time to 21 s for the normal-mode stimulus and 30 s for autostimulation: 21-s apnea has considerably less clinical relevance than 30-s apnea. The pulse width should be limited to 250 μs and the signal frequency to 20 Hz.

Indication for nocturnal modification of VNS therapy

Nocturnal reduction of VNS therapy intensity is by no means indicated in all VNS patients. Rather, this should be discussed (with reference to the lack of evidence from any later multicenter studies to date) with those patients in whom there is already clinical suspicion (or polysomno-graphic evidence) of a VNS-induced sleep disorder, as well as initially, before initiation of VNS therapy, in patients with SAS, in order to avoid worsening.

Practical conclusion

- Stable sleep is an important pillar in the overall concept of epilepsy therapy.
- The neurostimulation procedures (deep brain stimulation, DBS) at the anterior nucleus of the thalamus and vagus nerve stimulation (VNS) that have been approved for epilepsy treatment in Europe to date can severely disturb sleep microarchitecture and macroarchitecture as a side effect, possibly resulting not only in daytime sleepiness as well as cognitive and affective disorders but also in antagonization of the potential seizure-suppressing effects of these stimulation procedures.
- As possible solutions to this dilemma, a reduction in stimulation intensity at night and a shortening of stimulation ON time can be discussed for VNS; for DBS, a reduction in stimulation intensity at night, a change from pulsatile to continuous stimulation, or a change in localization of the active stimulation may be helpful.

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Declarations

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