Academic Year 2015 - 2017

THE INFLUENCE OF ANTIEPILEPTIC POLYTHERAPY AND VAGUS NERVE STIMULATION ON SLEEP IN PATIENTS WITH DRUG RESISTANT EPILEPSY

Céline SINATTI

Promotor: Prof. Dr. Paul Boon
Co-promotor: Dr. Stephanie Hödl

Dissertation presented in the 2nd Master year in the programme of MASTER OF MEDICINE IN MEDICINE
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PREFACE

This master thesis is a final milestone in my five-year journey of medical studies. Although the road was bumpy at times, it was a wonderful experience. Therefore, I’d like to say a special thanks to some people who supported me over the last five years and during this master thesis.

First, I would like to express gratitude to Prof. dr. Boon for giving me the opportunity to perform this research in the wondrous neuroscience field. I’m also forever indebted to Dr. Hödl, for her insights in medical and neurological issues and useful feedback. She provided motivation when needed and help when asked for and I’ll never forget the knowledge I acquired.

A special word of credit goes to Eng. Philip Taylor for his linguistic guidance. As a native speaker he helped me to refine the language I used.

Lastly, I would like to say a special thanks to my family and especially my parents and sister. Their ever-present warmth, many encouragements and unconditional faith mean the world to me.
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ABSTRACT

Epilepsy is one of the most prevalent neurological disorders, affecting over 50 million people worldwide. Most patients respond well to the currently available antiepileptic drug (AED) therapies. However, one-third will continue to experience long periods of uncontrolled seizures. These individuals are regarded as having drug resistant epilepsy. Some of these patients may benefit from neurostimulation of the nervus vagus (VNS), exerted via a stimulation device implanted under the left clavicle. Sleep problems and disorders are frequently found in epilepsy patients. Since sleep disturbances and epilepsy are both prevalent conditions in the overall population, comorbidity and reciprocal influence are very likely to exist. Several studies have already investigated the impact of nocturnal seizures, AED polytherapy and VNS on sleep-pattern, sleep-fragmentation and respiratory changes during sleep, in epilepsy patients. By searching through several medical and scientific databases, such as Pubmed and Web of Science, we analysed these studies and other currently available literature on these subjects. We concluded that all currently and commonly used AEDs seem to have effects on sleep structure. In order to optimize the management of epilepsy patients, it is important to be aware of these effects. In order to evaluate them, more prospective studies with larger sample size and focused on dose-response relationship are recommended. In addition, we found that VNS seems to reduce daytime sleepiness in most cases, even in subjects without reduced seizure frequency.
ABSTRACT NEDERLANDS

Epilepsie is een van de meest prevalente neurologische aandoeningen die wereldwijd meer dan 50 miljoen mensen treft. Het merendeel van de epilepsie patiënten reageert goed op de huidig beschikbare behandelingen met anti-epileptische medicatie (AED). Voor één derde van de patiënten volstaat deze medicamenteuze therapie echter niet waardoor zij onderhevig blijven aan langdurige episodes van ongecontroleerde aanvallen. Deze patiënten worden ‘drug-resistent’ genoemd. Sommige van deze drug-resistente patiënten kunnen geholpen worden via neurostimulatie van de nervus vagus (VNS), waarbij een stimulator, gelijkaardig aan een pacemaker, geïmplanteerd wordt onder de linker clavicula. Slaapstoornissen zijn een veel voorkomende aanverwante aandoening bij epilepsie patiënten. Aangezien zowel slaapstoornissen als epilepsie prevalent zijn, is er een grote waarschijnlijkheid op co-morbiditeit en wederkerige invloed van deze aandoeningen. Verschillende studies onderzochten reeds de impact van nachtelijke aanvallen, AED polytherapie en VNS, op slaapstructuur, slaapfragmentatie en respiratoire veranderingen (tijdens slaap) bij epilepsie patiënten. De in dit werk aangehaalde studies werden geselecteerd en geanalyseerd via het doorzoeken van verschillende medische en wetenschappelijke databases, waaronder Pubmed en Web of Science. Op deze wijze werd ook bijkomende literatuur betreffende deze onderwerpen bekomen. We zijn tot het besluit gekomen dat alle huidige veel gebruikte AEDs één of meerdere veranderingen teweegbrengen in de slaap(structuur) van epilepsie patiënten. Het is dan ook belangrijk ons van deze problemen te vergewissen in het kader van het streven naar een optimale zorg en aanpak voor de epilepsie patiënt. Om een beter inzicht te krijgen in de exacte mechanismen achter de invloed van de verschillende AEDs op de slaap(structuur), is er nood aan méér prospectieve studies, met grotere sample sizes, die focussen op de dosis respons relaties. Bijkomend hebben we vastgesteld dat VNS de neiging heeft om overdreven slaperigheid overdag te doen afnemen bij het merendeel van de patiënten, zelfs bij diegenen waar VNS geen vermindering in aanvalsfrequentie teweegbrengt.
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<th>Full Form</th>
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<tr>
<td>5-HT</td>
<td>Serotonine</td>
</tr>
<tr>
<td>AASM</td>
<td>American Academy of Sleep Medicine</td>
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<tr>
<td>ACh</td>
<td>Acetylcholine</td>
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<tr>
<td>AED</td>
<td>Antiepileptic Drug</td>
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<td>AHI</td>
<td>Apnea/Hypopnea Index</td>
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<tr>
<td>AMPA</td>
<td>Alpha-Amino-3-Hydroxy-5-Methyl-4-Isoxazole Propionic Acid</td>
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<td>BRV</td>
<td>Brivaracetam</td>
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<td>BZD</td>
<td>Benzodiazepine</td>
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<tr>
<td>CBSDA</td>
<td>Cardiac-Based Seizure Detection Algorithm</td>
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<td>Carbamazepine</td>
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<tr>
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<td>Clobazam</td>
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<td>Central Nervous System</td>
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<tr>
<td>CPAP</td>
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<td>Cerebral Vascular Accident</td>
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<td>DA</td>
<td>Dopamine</td>
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<td>EDS</td>
<td>Excessive Daytime Sleepiness</td>
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<td>EEG</td>
<td>Electroencephalography</td>
</tr>
<tr>
<td>EMG</td>
<td>Electromyography</td>
</tr>
<tr>
<td>EMU</td>
<td>Epilepsy Monitoring Unit</td>
</tr>
<tr>
<td>EOG</td>
<td>Electro-oculography</td>
</tr>
<tr>
<td>ESS</td>
<td>Epworth Sleepiness Scale</td>
</tr>
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<tr>
<td>FBM</td>
<td>Felbamate</td>
</tr>
<tr>
<td>FP</td>
<td>False Positive</td>
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<td>Fast Fourier Transform</td>
</tr>
<tr>
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</tr>
<tr>
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</tr>
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<td>GWS</td>
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</tr>
<tr>
<td>HFO</td>
<td>High Frequency Oscillation</td>
</tr>
<tr>
<td>IEA</td>
<td>Interictal Epileptiform Activity</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>--------------</td>
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<tr>
<td>IED</td>
<td>Interictal Epileptiform Discharge</td>
</tr>
<tr>
<td>IGE</td>
<td>Idiopathic Generalized Epilepsy</td>
</tr>
<tr>
<td>ILAE</td>
<td>International League Against Epilepsy</td>
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<tr>
<td>iTC</td>
<td>Ictal Tachycardia</td>
</tr>
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<td>LC</td>
<td>Locus Coeruleus</td>
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<td>LCM</td>
<td>Lacosamide</td>
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<tr>
<td>LEV</td>
<td>Levetiracetam</td>
</tr>
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<td>Lamotrigine</td>
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<tr>
<td>MSL</td>
<td>Mean Sleep Latency</td>
</tr>
<tr>
<td>MSLT</td>
<td>Multiple Sleep Latency Test</td>
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<td>MWT</td>
<td>Maintenance Wakefulness Test</td>
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<td>NFLE</td>
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</tr>
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<td>NREM</td>
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<td>Primary Generalized Tonic-Clonic (seizure)</td>
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<td>Phenytoin</td>
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<td>PLMS</td>
<td>Periodic Limb Movements in Sleep</td>
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<td>PNS</td>
<td>Peripheral Nervous System</td>
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<td>POS</td>
<td>Partial-Onset Seizure</td>
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<td>PPN</td>
<td>Perampanel</td>
</tr>
<tr>
<td>PSG</td>
<td>Polysomnography</td>
</tr>
<tr>
<td>QoL</td>
<td>Quality of Life</td>
</tr>
<tr>
<td>RAS</td>
<td>Reticular Activating System</td>
</tr>
<tr>
<td>RBD</td>
<td>REM (Rapid Eye Movement) Behaviour Disorder</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized Controlled Trial</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>REM</td>
<td>Rapid Eye Movement</td>
</tr>
<tr>
<td>RLS</td>
<td>Restless Legs Syndrome</td>
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<td>RUF</td>
<td>Rufinamide</td>
</tr>
<tr>
<td>SOREM</td>
<td>Sleep-Onset REM (Rapid Eye Movement)</td>
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<tr>
<td>SPECT</td>
<td>Single-photon Emission Computed Tomography</td>
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<tr>
<td>SV2A</td>
<td>Synaptic Vesicle Protein 2A</td>
</tr>
<tr>
<td>SWS</td>
<td>Slow Wave Sleep</td>
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<td>TGB</td>
<td>Tiagabine</td>
</tr>
<tr>
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<td>Topiramate</td>
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<tr>
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<td>Vigabatrin</td>
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<td>VN</td>
<td>Vagus Nerve</td>
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<td>Vagus Nerve Stimulation</td>
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<td>Valproic Acid</td>
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<td>ZNS</td>
<td>Zonisamide</td>
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</table>
INTRODUCTION

1. Relationship epilepsy - sleep

Self-reported sleep disturbances in people with epilepsy are about twice as prevalent as in healthy controls. Since sleep disturbances and epilepsy are both prevalent conditions in the overall population, comorbidity and reciprocal influence are very likely to exist (1). For instance, sleep disorders can lead to excessive daytime sleepiness (EDS), which is also frequently reported in people with epilepsy. Both conditions are known to induce a significant decrease in quality of life (QoL) and it is likely that the comorbidity of these disorders may cause an even greater deterioration in QoL. Sleep disturbances may interfere with seizure control in people with epilepsy. This deterioration in QoL is one of the main reasons why interaction between epilepsy and sleep is thoroughly studied. The first suggestion of an interaction between the sleep-wake status and the occurrence of seizures dates from 1885, when Gowers classified timings of seizure occurrence as diurnal, nocturnal or diffuse. Later, following the introduction of electroencephalography (EEG) and polysomnography (PSG), the interaction between epilepsy and sleep was studied more thoroughly, proving to have numerous aspects (1). Sleep can induce seizures and epileptic EEG abnormalities. In general, seizures and interictal epileptiform discharges (IEDs) are considered being facilitated during non-rapid eye movement (NREM) sleep and being suppressed during rapid eye movement (REM) sleep. The epileptiform EEG discharges during NREM sleep are thought being facilitated by the synchronized EEG pattern during those sleep stages, whereas in REM sleep characterized by desynchronized EEG pattern epileptic discharges are less likely to occur (1). The occurrence of seizures during sleep-wake cycle depends mostly on the seizure type and its etiology. For example, seizures in autosomal dominant nocturnal frontal lobe epilepsy (NFLE) only take place during sleep, whereas seizures in absence epilepsy only occur in the waking state (1). Sleep deprivation is also considered activating epileptiform activity, but it remains controversial whether these activating effects are due to increased neuronal excitability or simply due to induction of sleep. Furthermore, sleep deprivation seems to provoke seizures in several well-delineated epileptic syndromes and even in people without a prior history of seizures (1).
Both diurnal and nocturnal seizures are thought to disrupt sleep. Instability and reduction of REM sleep are most often reported (1). Also found are a shorter total sleep time and a decrease in sleep efficiency, next to an increase of sleep fragmentation, elongation of sleep latency and gain of stage shifts and awakenings. People suffering temporal lobe epilepsy have more severe sleep disorganization than those with extra-temporal foci and sleep structure is more disrupted during nights with seizures than in seizure-free nights (1).

In summary, the clinically important interaction between sleep and epilepsy is complex and mutual. Epilepsy itself and its therapy may disturb sleep. This may result in a chronic deprivation and fragmentation of sleep, which both have possible negative effects on seizure control, causing a vicious circle (1).

Multiple studies have been conducted in the last years in order to quantify the relationship between sleep disturbance and epilepsy. For example, a study of de Weerd et al. investigated in 2004 whether sleep disturbances are more frequent among patients with partial seizures compared to controls. Besides this, the authors evaluated what impact on QoL sleep disturbance may have in these patients. They established that sleep disturbance was more than twice as prevalent in the epilepsy patients (39% versus 18% in the control group) and that most domains of their sleep were significantly disturbed. People with epilepsy already tend to have a significant reduction in QoL, being reinforced by this sleep disturbance (2). In 2011, de Weerd conducted another study, in cooperation with van Golde et al., focusing on prevalence, impact on QoL and effects of treatment of sleep disorders on the course of epilepsy. Concerning the prevalence, a large difference between epilepsy patients and the control group was observed in measures of excessive daytime somnolence (13.8%) and psychiatric sleep disorders (14.1%). In other questionnaire-based studies, sleep complaints reported by adult epilepsy patients varied from 16.9% to 36% (1).
2. Normal sleep-patterns in non-epilepsy patients and neural mechanisms involved in sleep

2.1. Normal sleep patterns

Sleep can be defined as an active, rapidly reversible state of decreased responsiveness towards environmental stimuli, reduced motor activity and diminished metabolism. Humans spend around one-third of their life, corresponding to the average of eight hours sleep per night, sleeping. The exact purpose of sleeping is not yet fully understood, however various theories pretend that sleep provides important regenerative and recovery functions, as well as energy conservation and memory consolidation (3). This phenomenon of sleep is characterized by specific EEG changes in the function of the autonomic nerve system (4).

While being awake, the anterior EEG deflections in healthy adults show a rapid beta-activity (13-30 Hz), with a low voltage. When the eyes are closed, a slower (8-12 Hz), high voltage alpha-activity can be measured in the posterior parts of the brain. When opening the eyes, a desynchronization occurs. Alpha-activity is generated by a simultaneous firing of the neurons in the occipital lobes, who are, in their turn, controlled by the thalamus (4).

Generally, sleep consists of two main types of sleep that alternate cyclically about every 90 to 120 minutes: the REM and the NREM stages (5). The function of alternations between these two sleep stages is not yet fully understood, but irregular cycling and/or the absence of one of the stages are correlated with sleep disorders (6). The function REM sleep can be described as a period in which the brain is active and the body is paralyzed (except for eye movements, middle ear ossicles and respiration). During NREM sleep, the brain is less active but the body can move. NREM sleep amounts to approximately 75 to 80% of total time spent in sleep, REM sleep to the other 20 to 25% (6). NREM sleep is composed of 3 stages that are differentiated based on EEG characteristics. When ‘normal’ individuals first fall asleep, they enter NREM sleep stage 1 (N1) (sleep drowsiness). This stage is characterized by a decrease of alpha-activity, the ‘alpha drop-out’, and the occurrence of low voltage, slow waves, known as theta-activity (5-7 Hz) as well as vertex waves. The eye movements made during N1 are typically slow and rolling. Patients awaked from N1 do not perceive that they actually were asleep, which corresponds to the fact that stage N1 is the lightest stage of sleep. Then, they progress through stage 2 (N2) of the NREM sleep. This stage consists of vertex waves and of two typical N2 features: sleep spindles and K-complexes. Sleep spindles are short (though ≥0.5 s) and have an EEG frequency in the beta-band (mostly around 14 Hz). They occur most dominantly in the central EEG leads. K-complexes have a total duration of ≥0.5 s and are
well-delineated, negative, sharp waves that are immediately pursued by a positive component. K-complexes have their maximal amplitude in the frontal regions of the EEG. Stage 3 (N3) is often referred to as slow wave sleep (SWS) or delta sleep, because of its specific high amplitude (>75 µV), slow waves (0.4-5 Hz), called delta waves. It is more difficult to arouse sleepers during N3 when compared to N1 or N2, therefore this stage is also referred to as the ‘deep sleep stage’. SWS may last for a few minutes up to an hour, depending on the person’s age, before reversion back to N2. Shortly after this, the first REM sleep period begins, lasting about 15-20 minutes and is followed by another NREM cycle. This alternating pattern continues throughout the night, but as the night progresses N3 becomes less apparent and the periods of REM sleep grow longer (6, 7). REM sleep consists of three main characteristics, demonstrated by typical EEG, electro-oculography (EOG) features. EEG shows a low-voltage, mixed EEG pattern with sawtooth waves (2-6 Hz) that are sharply contoured and that occur in short flares. The defining feature of REM sleep is demonstrated on EOG: conjugate, irregular, sharply-peaked, rapid eye movements, that have an initial phase of <500 ms. Lastly, electromyography (EMG) shows that there is an inactivity of all voluntary muscles (except for, as mentioned above, extra-ocular muscles, middle ear muscles and the diaphragm). This phenomenon, called atonia, results from direct inhibition of α-motor neurons (5).

Sleep can objectively be quantified by PSG investigations, examining EEG signals, eye movements, muscle activity, leg movements, respiration (nasal flow, thoracic and abdominal respiratory movements) and oxygen saturation during the whole night. Based on these results, the different sleep stages can be determined and can graphically be presented as a ‘hypnogram’ (4).
2.2. Neural mechanisms involved in sleep

As previously mentioned, sleep is an active process, which implies several structures of the brain stem and diencephalon. Cholinergic (Ach) neurons in the reticular activating system (RAS) regulate desynchronization of the EEG while being awake and during REM sleep, but also initiate the REM sleep. On the other hand, the serotonergic (5-HT) neurons of the raphe nucleus suppress REM sleep and are involved in terminating the REM stages. Furthermore, noradrenergic neurons in the locus coeruleus (LC) are responsible for the decrease in sensitivity of the spinal motor neurons, leading to the atonic features during REM. Finally, neurons in the pre-optical and supra-chiasmatic nuclei of the hypothalamus play an active role regulating sleep-wake rhythm (4).
3. Epilepsy

Epilepsy is a high prevalent, chronic neurological condition, affecting over 50 million people worldwide (10). The disorder is characterized by recurrent spontaneous epileptic seizures, defined as transient periods of excessive and/or hypersynchronous activity of neurons in the brain. These seizures are usually self-limiting and can be preceded by an aura as visual, auditory, olfactory, gustatory changes or abdominal discomfort. It is important to mention that the terms ‘seizures’ and ‘epilepsy’ should not be used interchangeably: seizures are symptoms, whereas epilepsy is a disease characterized by recurrent seizures (11). Moreover, the prevalence of epilepsy is about 0.5% but the lifetime risk of having an epileptic seizure varies between 5 and 10% (4). Epileptic syndromes are defined by plural factors, as seizure type, age of onset, family history, and findings at physical examination, ictal and intra-ictal EEG and neurologic imaging. Each syndrome has its own prognosis and specific drugs to which it is most likely to respond. This way, the definition and terminology of epileptic syndromes directly implies the prognosis and treatment and simplifies communication between health workers (12).

The exact etiological mechanism of epilepsy is not known. However, 25% of the patients shows an underlying cause such as brain tumors, vascular brain lesions, congenital deformations of the brain, brain injuries, cerebral vascular accidents (CVA), infections of the central nervous system (CNS) or degenerative disorders. Besides these, several metabolic conditions, intoxications and abuse of alcohol, tranquillizers and sedative drugs may provoke epileptic seizures (4).

METHODOLOGY

This section outlines the search strategy and selection criteria adopted for this literature study and provides descriptions of the types of studies that were reviewed.

1. Study description

Given the fact that randomized controlled trials (RCT’s) provide the best evidence, all RCT’s concerning drug-resistant epilepsy and sleep, vagus nerve stimulation and sleep, and AED and sleep, meeting the selection criteria, were incorporated.
2. Selection criteria for articles

Due to the large amount of publications obtained, the next step was a detailed examination of the articles to judge if they were adequate for inclusion in this literature study. This was performed by a qualitative assessment of their relevance and innovative character, the year of publication (2000-present) and the journal in which they were published (impact factor). This last criterion was fulfilled by adding ‘core clinical journals’ as a search filter. Furthermore, studies concerning children and animals were excluded, as well as articles that were not written in English, Dutch, French or German. Studies with methodological weaknesses arising from small convenience samples, few factors measured, or weak data analysis, were included only when they provided insights not available from more rigorous studies.

3. Search strategy

Before starting the search for articles eligible for inclusion in this study, a profound orientation in the subjects of epilepsy, antiepileptic drugs (AED) and vagus nerve stimulation (VNS) was performed. This by searching the Ugent library database for publications of Prof. Dr. Boon and Prof. Dr. Vonck concerning these themes. Additionally, the Ugent library database was also explored for doctoral dissertations and theses regarding these three related topics.

In order to obtain research material relevant for incorporation in this study, medical and scientific databases as “Pubmed” and “Web of Science” were searched. To ensure that significant studies were not missed, the search terms remained broad and articles were selected from the databases by entering different combinations of the following terms: “polytherapy, AED, VNS, epilepsy, sleep, polysomnography, comorbidity, OSA, perampanel, brivaracetam.” Following the “serendipity method” more articles were retained based on references and citations of the selected publications.

The introductory part regarding ‘the normal sleep patterns and neural mechanism involved in sleep’ was written based on information received during lectures at the University of Ghent. These lectures were presented by Prof. Dr. Boon in October 2013 and dealt with the following topics: the reticular formation, sleep and EEG.
## 4. Pubmed

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17 more articles were obtained by the serendipity method.
5. Database Ghent University

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An additional 72 articles were obtained by the serendipity method.

In total, 109 articles were incorporated in this literature study.

Note: Sometimes we were forced to include articles published before 2000, due to the lack of more recent, available literature.

RESULTS

1. Sleep EEG in epilepsy patients

As mentioned above, epileptic seizures are thought to disrupt sleep. Reported in the past are a disruption and lability of REM sleep, less total sleep time, longer sleep latency, reduced REM sleep and an increase in stage shifts and awakenings (1, 13). Klobučníková and Kollár also reported a statistically significant, higher amount of N2 sleep in epilepsy patients when compared to a healthy control group (14). Foldvary-Schaefer reviewed the in 2000 available literature on the influence of seizure-type on sleep EEG. She concluded that nocturnal generalized seizures decrease total sleep time, as well as REM sleep, they prolong REM latency and increase sleep fragmentation. They augment time spent in N1 sleep and decrease N2, while SWS (N3) remains stable. REM rebound (an increase of REM sleep duration after periods of REM suppression, inducted by, for example, sleep deprivation) was not stated later in the night after a seizure or during subsequent seizure-free nights. Isolated, focal nocturnal seizures have little impact on sleep. However, when multiple seizures occur during the night, a decrease in REM sleep and duration of REM periods is observed. Daytime seizures seem to
result in a significant reduction of REM sleep in the following night, while NREM is not affected (14).

As previously mentioned, NREM sleep, as well as its deficit, can facilitate seizures and IEDs, with a more thorough effect on diffuse discharges. A study of Fausher et al., conducted in 2014, tried to provide a mechanistic explanation for this phenomenon. Knowing that cortical slow waves (<1 Hz), consisting of a deactivated (‘down’, hyperpolarized) and an activated (‘up’, polarized) state, are present during the NREM stage, they investigated the influence of these waves (and the role of the ‘up’ and ‘down’ stages) on human focal epileptic activity. Due to the fact that the ‘up’ state of the slow waves augments physiological rhythms, the investigators hypothesized that sleep slow waves, and particularly their ‘up’ state, are the specific components of NREM sleep mediating activation of epileptic activity. For this investigation, 8 patients with drug resistant focal epilepsies underwent a combined scalp-intracerebral EEG. Fausher et al. analysed 259 frontal EEG channels and marked 442 epileptic spikes and 8487 HFOs during high amplitude widespread slow waves and during matched control segments with low amplitude widespread slow waves, non-widespread slow waves or no slow waves during the same sleep stages. The results of the study showed that there were more spikes and high frequency oscillations (HFOs) during slow waves than during control segments (79% of spikes during slow waves and 65% of HFOs). Moreover, the spike and HFO density also increased for higher amplitude slow waves. When comparing the density of spikes and HFOs during the ‘up’ and the ‘down’ states, their density seemed to be the highest during transition from the ‘up’ to the ‘down’ state. This is in contrast to physiological EEG rhythms in normal channels, which, as discussed earlier, peak during the ‘up’ state. This evidence suggests that in the epileptic brain periods coinciding with high synchronization are associated with increased occurrence of interictal spikes and HFOs, rather than periods coinciding with hyperexcitability. Finally, the study demonstrated that HFOs in channels with normal activity peaked differently during slow wave cycle compared to HFOs in channels with epileptic activity: whereas the HFO density peaked at the beginning of the ‘down’ state in case of channels with epileptic activity, HFO density peaked at the transition to the ‘up’ state in channels with normal activity. This difference in distribution pattern might allow for a differentiation between physiological and pathological HFOs and could be used to improve the localization of seizure onset, especially in brain areas in which physiological
HFOs are present (such as the paracentral areas, the hippocampus and the occipital cortex) (15).

On the other hand, multiple studies have confirmed that seizures barely occur during REM sleep: the proportion of seizures amounts to only 1% or less. In 2013, Marcus Ng. and Milena Pavlova investigated the impact of REM sleep on seizures. Therefore, they reviewed 42 independent conventional and intracranial studies, including a total net of 1458 patients. Adjusted for duration, they established that REM sleep was the most protective sleep stage against both focal and generalized seizures and against focal interictal discharges. Marcus and Pavlova, and several other studies (16), explain this phenomenon by a maximally desynchronized EEG pattern during REM sleep, reducing the likelihood of spatial and temporal summation of aberrant depolarizations. Moreover, REM sleep seemed to have an extra protective impact when compared to wakefulness: focal seizures would occur averagely 7.38 times less during REM sleep, generalized seizures 3.25 times and focal interictal discharges 1.11 times. This could be clarified by recent connectivity studies, revealing a further strategic loss of connectivity in REM sleep, accounting for its unique antiepileptic impact on seizures. Lastly, further studies have demonstrated that REM sleep may be useful in localizing epileptogenic foci. Several studies have explored this localizing ability of REM sleep but the most powerful arguments were found in two independent studies by Ochi et al. (17) and Malow and Aldrich (18). They respectively evaluated a subset of tuberous sclerosis patients and a single temporal lobe epilepsy patient. In 6 of Ochi’s patients, the semiology, neuroimaging, and other EEG were discordant in localizing the epileptogenic focus. Focal resection was undertaken in the hemisphere to which discharges were selectively lateralized in REM sleep. Four of 6 subjects did well after surgery. In Malow’s case report, 1 patient with bitemporal discharges selectively lateralized in REM sleep. After amygdalohippocampexomy in this hemisphere, the patient was rendered seizure-free for at least 3 years. For patients of both studies, lateralization based on REM sleep alone was able to localize the epileptogenic zone in the midst of discordant data and predict seizure freedom (19, 20). Due do this, dedicated sleep recordings may be useful in presurgical evaluation in drug resistant patients. However, there is still controversy regarding the localizing value of interictal discharges (19). For example, in Lieb’s study (20), 2 of 10 patients with REM-lateralized discharges were discordant with the final localization.
2. Sleep disorders in epilepsy patients

Daytime sleepiness is defined as the inability to stay awake during waking episodes of the day (14). It results in unintended episodes of sleep or drowsiness (a decreased level of consciousness characterized by sleepiness and difficulty in remaining alert but easy arousal by stimuli (21)). These sleep episodes are mostly only present during times of rest or when little attention is required. Sometimes, daytime sleepiness is correlated to an increase of total amount of sleep, without the feeling of full recovery and restoration. Excessive daytime sleepiness (EDS) is a chronic symptom, occurring for at least 3 months prior to diagnosis. EDS is defined by the International Classification of Sleep Medicine third Edition (ICSD-3) as ‘a subjective report of difficulty in maintaining the alert awake state, usually accompanied by a rapid entrance into sleep when the person is sedentary’. Excessive sleepiness may lead to an excessively deep or prolonged major sleep episode. It can be quantitatively measured by use of subjectively defined rating scales of sleepiness or physiologically measured by electrophysiologic tests such as the multiple sleep latency test (MSLT). Excessive sleepiness most commonly occurs during the daytime, but it may be present at night in a person, such as a shift worker, who has the major sleep episode during the daytime (22). It also may be a side effect of several drugs, for example AEDs (14). Below, an overview is given of sleep disorders that are commonly found in epilepsy patients and may lead to EDS.

Currently, the relationship between obstructive sleep apnea syndrome (OSAS) and epilepsy has been investigated extensively. OSAS is a relative frequently found condition in middle age obese men. The disorder manifests when plural collapses of the upper airways occur during the night, causing desaturation moments and reactive arousals. When these arousals appear frequently, sleep fragmentation and complete disturbance of the normal sleep structure (basal structural organization of normal sleep build up by REM sleep and NREM sleep stages (6)) take place (4). Available evidence in literature indicates that occurrence of OSAS in patients with epilepsy is not infrequent and even higher than in the general population. Treatment of OSAS with continuous positive airway pressure (CPAP) seems to improve seizure control in people with epilepsy (23). A systematic, clinical and PSG investigation of unselected adult epilepsy patients –conducted in 2003 by Manni et al.- has reported an OSAS prevalence of 10.2% (8). Another PSG study of Malow et al. found prevalence up to 30% of previously undiagnosed OSA among a group of drug resistant epilepsy patients. This prevalence rate seems to be very high in comparison to non-epileptic patient populations. The
exact reasons for this remarkable difference in prevalence rate are unclear, but a significant role of iatrogenic practices should not be ignored. Presumably, treatments with AEDs as lamotrigine (LTG), felbamate (FBM) and levetiracetam (LEV) and/or VNS, influence OSAS (24).

OSAS, in its turn, may have adverse effects on several features of epilepsy such as daytime sleepiness, mood disorders, cognitive impairment, QoL and seizure control. This last aspect has been investigated by several studies, providing evidence that OSAS can lead to a higher frequency of seizures. The study of Manni et al. showed a later onset of seizures and more frequently experienced seizures during sleep. OSAS may enable seizure occurrence by increasing arousals during NREM sleep and inducing daytime sleepiness (25).

Two other studies focused on symptoms of the restless legs syndrome (RLS) and -in PSG studies- on the occurrence of periodic limb movements during sleep (PLMS) in epilepsy patients. These studies, published by Malow et al. in 1997 and by Kathami et al. in 2006, suggested that symptoms of RLS were not significantly more prevalent in people with epilepsy in comparison to a control group. However, a good estimate on the prevalence of RLS in epilepsy patients cannot be based on these results. This is due to the fact that both studies used a single question addressing RLS that did not cover all criteria for this diagnosis. Concerning PLMS, Malow et al. observed a high PLMS index (>20) in 17% of epilepsy patients. However, many of these PLMS didn’t lead to arousals or awakenings and none of the patients needed treatment. Moreover, there was no information available on the presence or absence of RLS symptoms in these patients (1).

There is some evidence available suggesting that REM sleep behavior disorder (RBD) is linked to epilepsy, mainly in elder epilepsy patients. As both disorders are more frequent in older age, these conditions could co-occur by chance in the elderly. However, a common pathophysiology may be hypothesized: both epileptic seizures and RBD might be due to neurodegenerative processes in the brain or to vascular cerebral lesions. Furthermore, it can be speculated that RBD might facilitate sleep-related seizures through the disruption and partial deprivation of REM sleep. Lastly, it is important to mention that RBD is known to mimic focal seizures (specifically frontal and temporal lobe seizures), potentially leading to a misdiagnosis of epilepsy (1).
**NREM sleep parasomnias** such as sleepwalking, night terrors and confusional arousals are very frequently reported in patients with NFLE (25). However, no systematic PSG studies investigating the co-occurrence of both disorders are known. On the other hand, it should be mentioned that some data are available on a final common pathway for both disorders, but more studies should be performed to further establish these comorbidities. In analogy to RBD and epilepsy, this comorbidity is challenging from a diagnostic point of view as NREM arousal parasomnias can be difficult to distinguish from temporal lobe and especially frontal lobe nocturnal seizures (1).

The most common sleep disorder, affecting 10% of the general population, is called *insomnia*. This condition is characterized by quantitatively and/or qualitatively insufficient sleep to ensure normal functioning during the day (4). Although questionnaire-based studies suggest a prevalence of insomnia in people with epilepsy up to 52%, no literature was found on PSG studies assessing this comorbidity (1).

Circadian rhythm and epilepsy are known to interact and *circadian rhythm sleep disorders* are seen in people with neurodevelopmental disorders who often also have epilepsy. However, no studies have been conducted to measure the prevalence of circadian rhythm sleep disorders in people with epilepsy (1).

### 3. Diagnostic evaluation of sleepiness in patients with epilepsy

When evaluating subjective reported sleepiness in epilepsy patients, it is extremely important to obtain an accurate 24-hour-sleep-wake history. Furthermore, other relevant history factors as medical history, type and frequency of epileptic seizures, their incidence correlated to the circadian cycle and actual AED therapy and the use of other drugs, should be evaluated. In addition, social, environmental or psychological conditions, that could interfere with sleep quality, should also be taken into account. In some epilepsy patients, cerebral lesions may be the cause of sleep problems, therefore neurological examination and magnetic resonance imaging (MRI) could also be recommended. Standard EEG during daytime and overnight-EEG could detect abnormalities in EEG activity and (inter)ictal epileptic discharges, that may cause micro-arousals and fragmentation of sleep, leading to sleep disorders as hypersomnia (14).

In order of providing a subjective measure of daytime sleepiness, the Epworth Scale Sleepiness (ESS) is widely used. This is a self-administered questionnaire consisting of eight
questions. Respondents are asked to rate, on a 4-point scale (0-3), their usual chances of dozing off or falling asleep while engaged in eight different activities. Most people engage in those activities at least occasionally, although not necessarily every day. The ESS score (the sum of 8 item scores, 0-3) can range from 0 to 24. The higher the ESS score, the higher that person’s average of daytime sleepiness. An ESS score greater than 10 is considered suggestive of EDS. However, the exact clinical significance of the ESS and its cutoff for daytime sleepiness are not well established (26).

For quantification and refinement of subjective reports of sleep disturbances in epilepsy patients, two objective measurements are widely used: the Multiple Sleep Latency Test (MSLT) and the Maintenance Wakefulness Test (MWT) (16). MSLT is a standard clinical and research procedure consisting of a full-day test that includes 5 scheduled naps separated by two-hour breaks. Once the lights go out, the test measures how long it takes before patients fall asleep. The average of these timeframes over all the naps is defined as the mean sleep latency (MSL) (26). A MSL of <5min is generally considered to be indicative of sleepiness, whereas a latency of >10 min is indicative of normal alertness (14). The protocol of the MWT is analogous to that of the MSLT, with that difference that subjects need to try to stay awake without using excessive mental or physical methods, while sitting upright in a darkened room. So, the MWT examines an individual's ability to stay awake in an environment of decreased sensory stimulation. Initially, the MWT was composed of 4 equally spread 20-minutes trials. Later on, in the evaluation of OSAS patients, the MWT were lengthened to 40 minutes. Currently, both trial lengths are used, depending on the patient’s degree of clinically reported sleepiness (27).

4. Drug resistant epilepsy

Once two or more unprovoked seizures have occurred, the diagnosis of epilepsy is retained and drug treatment is established. Most patients respond well to the currently available antiepileptic drug (AED) therapies. However, one-third will continue to experience long periods of uncontrolled seizures. These individuals are regarded as having drug resistant epilepsy. Drug resistant epilepsy is defined by the International League Against Epilepsy (ILAE) as ‘failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapy or in combination) to achieve sustained seizure freedom’. These patients can be referred to a Reference Centre for Refractory Epilepsy, where alternative treatments can be offered. These therapies include among others, epilepsy surgery.
and vagus nerve stimulation (VNS). To choose the most adequate alternative treatment, it is important to distinguish localized from generalized epilepsy. Localized epilepsy is caused by focal disease, whereas general epilepsy is caused by a disease that affects the entire cortex (28). The main treatment for patients with drug resistant epilepsy and an accurately identifiable limited focus is epilepsy surgery. It is the only treatment that can potentially cure epilepsy by removing the site that initiates the seizures. Drug resistant patients suffering from generalized epilepsy or patients who are not eligible for surgery can benefit from VNS-implantation (12).

5. VNS implantation

VNS is the stimulation of the vagus nerve (VN) with electrical pulses. VNS can be used to treat epilepsy and depression and investigations are being conducted to check its effectiveness in the treatment of Multiple Sclerosis and Alzheimer’s disease (29).

The VN is the 10th cranial nerve and is attached to the brainstem in the neck. It is a mixed nerve, consisting of both afferent and efferent fibres. The efferent fibres innervate several parts of the body as the heart, aorta, lungs and the gastrointestinal tract and count for about 20% of the fibre content of the VN. The afferent fibres, counting for the other 80%, lead information originating from these organs to the brain (29, 30).

The stimulation device, similar to a cardiac pacemaker is implanted under the left clavicle, distal to the branching of the recurrent laryngeal nerve. Then, two helical bipolar stimulating electrodes are placed around the left VN in the neck area. Always the left, never the right, nerve is used in order to limit the risk of bradycardia or arrhythmias (29, 30).

Until today, the exact mechanism of action of VNS is not fully unraveled, but several studies have uncovered the influence of the afferent and efferent fibers. It is generally accepted that the afferent fibers are crucial for the epilepsy suppressing effect whereas efferent fibers are thought to generate side effects (29, 30).

Due to the multiple and widespread connections of the VN, unilateral stimulation of the nerve is regarded to influence a large part of the brain, including the brainstem and intracranial structures in both hemispheres. Firstly VNS induces vagal input to the brainstem, affecting the nucleus of the solitary tract. This nucleus projects into the parabrachial nucleus (PBN), based in the dorsal pons, lateral to the LC. Furthermore, the PBN has far-reaching
connections to the thalamus, the basal forebrain, the hypothalamus and the cerebral cortex. The PBN is thus considered as an important target for VNS and may be responsible for mediating the antiepileptic effects of VNS on cortical and subcortical networks. Two major networks affected are the LC- norepinephrine (NOR) system and the Ach system (26). Concerning the LC-NOR system, the PBN receives afferents from the LC, a primary source of NOR. Other neurotransmitters involved in the LC-NOR system are Gamma-Amino-Butyric Acid (GABA) and 5-HT. GABA receptor cell death was shown being reduced due to VNS as well as conservation of the GABA receptor neuron density (31). On the other hand, regarding the Ach network, the PBN receives afferents from the two major sources of Ach in the brainstem: the pedunculopontine and lateral dorsal tegmental nuclei in the dorsal pons (26). As for the intracranial structures, increased blood flow in Positron Emission Tomography (PET) scan demonstrated involvement of the thalamus (32). A recent study, conducted in 2011 by the study group of Prof. Raedt (UZ Gent) et al., also found an increase of NOR in the LC region. However, the study was performed with rats, so further research in humans is recommended (33). More research also proved that the bilateral orbitofrontal and parieto-occipital cortex, the left temporal cortex and the left amygdala are areas of significant activation in response to VNS (32).

Regarding the antiepileptic action of VNS, it was suggested that seizures were suppressed in the cortex by a desynchronizing neuronal activity, exerted by VNS via the RAS. However, this interpretation has never been clearly documented in humans (34). The above mentioned study of Raedt et al., provided powerful evidence that there is a strong causal link between increased NOR signalling and the anticonvulsant effect of VNS. This is based on the following three major findings of the study: (I) VNS increases the concentration of NOR (not dopamine (DA), 5-HT or GABA) in the extracellular hippocampal region, (II) VNS prevents the development of pilocarpine-induced limbic seizures only in rats where VNS-induced increase of hippocampal NOR amounted to 70% or more and (III) selective $\alpha_2$-adrenoreceptor antagonism in the proximity of the seizure focus eradicates the seizure-suppressing effect of VNS. However, as mentioned before, the study was conducted in rats and these findings have not yet been confirmed by studies performed in humans (33).

Contingent upon the stimulus parameters used (see below), VNS is thought to be able to induce EEG synchronization (using low frequencies) and desynchronization (using high frequencies). However, other investigations suggested that the EEG response to VNS is more
likely to be related to the differential activation of specific ‘synchronogenic’ or ‘desynchronogenic’ fiber groups of the VN, than to stimulation parameters (34).

Figure 3. VNS device. Adapted from (35)

Figure 4. The LC and NOR system in the human brain. Adapted from (36)
6. The treatment of epilepsy with VNS

VNS is a worldwide-accepted alternative or adjunctive treatment for patients with medically resistant epilepsy who cannot benefit from epilepsy surgery. VNS is designed to prevent seizures by sending regular, mild pulses of electrical energy to the brain via the VN. The efficacy of VNS seems to be established for focal-seizure types but there is evidence that it has efficacy for other seizure types as well. Hence, VNS can be considered to be a broad-spectrum treatment (30).

It was investigated whether VNS has antiseizure (abort seizures), antiepileptic (suppressing seizures, preventative effect) and/or antiepileptogenic effects (reverse the development of the process, protective effect). Therefore, electrophysiological, functional and anatomical brain imaging and neuropsychological and behavioral studies have been conducted. Given its effective use in clinics, VNS clearly has an antiseizure effect. Interestingly, it was found that VNS also influences seizures in off-time (see below), suggesting an antiepileptic effect. Pulsed stimulation also reduced seizure frequency in the off-periods and stimulation effects outlasted the stimulation period. Since seizures reoccur after battery life ended, VNS is being considered as not antiepileptogenic (38).
Most commonly, a 30 s train of impulses (on) every 5 min (off) is given, but many clinicians use rapid cycling of 7 s on and 0.2 s off, increasing the amount of stimulation given daily. The pulses have a frequency of 20 to 30 Hz and a pulse width of 250 to 500 µs. The starting level of stimulation is 0.25 mA, increased to 1.25 to 2.00 mA over several weeks. However, it should be mentioned that the optimum current can vary among individuals and thus optimum VNS settings are still unknown (29, 30).

The positive effects resulting from VNS treatment do not occur immediately, but increase typically over 18 to 24 months. Most studies report subjective improvements in various QoL measurements, confirmed by objective trials. VNS has some mild to moderate acute and long-term use side effects. However, these side events are mainly stimulation related and reversible, tending to decrease over time. So most of them are predictable and related to stimulation variables. The acute complications concern most usually infections, vocal-cord pareses and lower facial weakness (30). The most common adverse events related to long-term use are stimulus-related coughing, throat pain and hoarseness. CNS side effects as nervousness, irritation, psychomotor slowing and tiredness have only seldom been reported, so they are not considered as major fallouts of VNS (30). During the implantation itself, intraoperative lead testing may lead to bradycardia, ventricular asystolia or complete heart block. Only rarely have these emerged years after VNS initiation (39). Furthermore, no idiosyncratic side effects have been reported yet (30). Lastly, VNS does not interact with AEDs (30), so both treatment types may be combined in order to achieve a better seizure control. Currently, investigations are conducted to evaluate the effect of the combination of VNS and the new AED perampanel (PPN) in patients with drug resistant epilepsy. For example, a very recent study (January 2016) by Juhl et al. evaluated effectiveness and safety of PPN as add-on treatment in 22 patients suffering drug resistant focal epilepsy. Seven of these patients had a VNS device, without the desired effect of seizure-reduction (the other patients had been previously submitted to epilepsy surgery, were under evaluation for surgery, had declined epilepsy surgery or had tried ketogenic effect, all four also without effect). After a 12-month during add-on treatment with PPN, the authors suggested that PPN could achieve important clinical improvement, or even seizure freedom in > 25% of these drug resistant focal epilepsy patients. However, these findings still need to be confirmed by new studies in a ‘real-life setting’ and further exploration regarding possible psychiatric adverse effects is recommended (40).
VNS is mainly used for chronic intermittent electrical stimulation of the left VN. However, through use of a magnet, VNS is also capable to deliver acute, on-demand activation of stimulation, providing acute seizure-abortion (41). So, the ‘magnet mode’ enables the patient and caregivers to provide immediate on-demand stimulation by passing the magnet, worn by the patient with a wristband or belt clip, over the pulse-generator. This magnet mode is used in addition to regular, intermittent, electrical stimulation provided by the ‘normal mode’. Since there is relatively little information on the role of magnet-induced stimulation in the management of recurrent seizures, Tatum et al. reviewed the literature available in 2009 and shared their clinical experience with magnet-induced VNS. They concluded that the use of the magnet virtually has no disadvantages concerning safety or overdosing. External application of the magnet may abort or lessen the intensity of an oncoming seizure and diminish the postictal period (41). However, it is important to take in account that some epilepsy patients are unable to use the magnet due to clinical seizure symptoms, physical limitations, cognitive impairment or nocturnal seizures. For these patients, automated seizure detection that triggers VNS could offer a solution. EEG and ECG studies have demonstrated that in an average of 82% epilepsy patients, ictal heart rate increases occurs (42). Boon et al. investigated recently (article was published in August 2015) for the first time in an epilepsy monitoring unit (EMU) setting, the performance of a novel cardiac-based seizure detection algorithm (CBSDA) incorporated in a VNS device (Aspire SR®, Cyberonics, Houston, Texas, USA). Besides the standard open-loop VNS, this device provides an automatic stimulation feature, triggered in response to ictal heart rate increases of ≥20%, delivering VNS in a closed-loop fashion. This automatic stimulation feature has the same stimulation waveform as open-loop VNS, although output current, stimulation duration and pulse-width can be set independently. Both open and closed-loop modes can be delivered in combination (43). The study of Boon et al. was a prospective, multi-center study for which 35 VNS candidates with a history of ictal tachycardia (iTC) were enrolled. iTC was defined as a 55% or 35 bpm increase in heart rate, to a minimum level of 100 bpm. The main purpose of the study was to demonstrate a seizure detection sensitivity of ≥80% for iTC seizures by at least one threshold setting, and to investigate false positive (FP) rate. The authors concluded high seizure detection when the appropriate threshold was applied, and the FP seemed to be acceptable (43). However, this conclusion should be interpreted with caution due to the fact that only 11 seizures associated with iTC were captured during the EMU.
7. Drug resistant epilepsy – AED and their effect on sleep in this patient population

With the release of thirteen new AEDs, the number of potential therapeutic interventions has exponentially increased over the last twenty years. Despite this remarkable increase, current principles governing drug therapy have not enormously changed over time. There are now twenty-four AEDs approved by the Food and Drug Administration for use in epilepsy in the United States and even more options are available in the rest of the world. (6) The main goal of current AED treatments is to achieve complete seizure freedom with no (or acceptable) side effects and to maintain a normal lifestyle. When seizure freedom cannot be achieved, the ultimate goal is the best possible QoL, obtained through a compromise between reduction in seizure frequency or severity and the burden of side effects.

When the decision to start a medication treatment is made, monotherapy is usually preferred over drug combinations based on following assumptions: monotherapy is associated with higher compliance, less side effects, reduced likelihood of interactions with other drugs, less potential teratogenic effects and a higher cost-effectiveness ratio.

Today, 59% of patients with newly diagnosed epilepsy become seizure-free on AED monotherapy. Another 5% needs a combination of drugs to have a complete control of their seizures. For choosing an adequate drug combination, several rationales should be taken into account. In this respect, it is important to consider the seizure type and syndrome classification, the patient’s age, gender, use of other drugs and comorbidities. Furthermore,
clinical and laboratory evidence suggests that for some AEDs it is recommended to combine them with other AEDs that have a different mechanism of action, in order to obtain additive or synergistic effects. The British National General Practice Study of Epilepsy reported that 27% of patients taking duo-therapy became seizure free, whereas for patients taking 3 AEDs this fraction is 10%.

It is becoming more and more apparent that several AEDs have multiple cellular effects that are not yet fully understood. However, with more information available regarding the pathophysiology of seizures, three broad mechanism of AED action are preserved: (I) modulation of ion channels (modification of cellular excitability), (II) increase in inhibitory neurotransmission (GABA-ergic) and (III) decrease in neuronal excitation (glutamatergic system) (45).

In 2009-2011 five new AEDs have been approved: vigabatrin (VGB), rufinamide (RUF), lacosamide (LCM), clobazam (CLB) and ezogabine (EZG). Due to side effects, limited-spectrums or high expense, LCM is the only novel medication that is currently used. Besides down regulating Na⁺ channel excitability, LCM also binds to collapsing-response mediator protein 2. LCM has positive effects in adults with uncontrolled partial seizures and its intravenous formulation expands options for patients who are unable to receive oral medication. Further studies are required to determine whether the drug is more effective compared to older AEDs (46).

Over the last five years, the efficacy and safety of brivaracetam (BRV) and PPN (40), two new possible AEDs, have been investigated multiple times in order to assess if these drugs are eligible to be launched on the market. A randomized controlled trial conducted by French et al. in 2010 provides preliminary class I evidence that adjunctive BRV is efficacious and well-tolerated in patients aged 16-65 years with partial-onset seizures (POS) (47). BRV is the 4-n-propyl analogue of LEV, so it is believed to, similarly to its analogue, act by binding the synaptic vesicle protein 2A (SV2A) (48). Another randomized trial done by French et al. in 2015 provides class I evidence for the fact that adjunctive PPN reduces primary generalized tonic-clonic (PGTC) seizure frequency, compared with placebo, in patients with drug resistant PGTC in idiopathic generalized epilepsy (IGE). However, nowadays, it is still only used as add-on medication for focal epilepsy (49). Perampamel acts as a selective non-competitive antagonist of the Alpha-Amino-3-Hydroxy-5-Methyl-4-Isoxazole Propionic Acid (AMPA) receptors, the major subtype of ionotropic glutamate receptors (50).
Given the numerous available AEDs for the management of epilepsy, when selecting the most suitable drug for the patient the following should be considered: (I) proven efficacy of the AED for the patient’s epilepsy seizure type or syndrome, for patients with epilepsy of unclear classification, an AED with a broad spectrum (for example LTG) is recommended, (II) patients taking co-medication with lipid-soluble agents, should avoid using AEDs with enzyme inducing activity, (III) with regard to safety and tolerability, it is in most cases advised to start the AED(s) in a low dose that is slowly titrated, (IV) for people who develop adverse effects or who experience problems with being compliant, decision making in a new drug choice can be guided by plasma concentration monitoring, (V) for patients who are not receiving an antiepileptic treatment yet and who suffer from high seizure density, an AED that can rapidly be titrated to a therapeutic dose (LEV) is preferred, (VI) for people who have swallowing difficulties, adequate formulations as syrups, liquids, crushable tablets and sprinkles are available, (VII) sodium valproate is discouraged in girls and women of childbearing age because of its association with fetal malformations, weight gain, polycystic ovary syndrome (PCOS) and cognitive problems, and (VIII) elderly have seizure freedom rates up to 80% when developing epilepsy in later life and so usually respond well to AEDs.
therapy; it is important to apply a slow titration schedule with a low target dose, considering the age-related changes in pharmacokinetics and pharmacodynamics, as well as the complications from comorbidities and problems with co-medication; so well-tolerated AEDs with a low potential for drug interactions (LTG, LEV and gabapentin (GBP)) should be selected (45).

Table 1. Efficacy of antiepileptic drugs against common seizure types and epilepsy syndromes. Adapted from (45)

<table>
<thead>
<tr>
<th>Antiepileptic Drug</th>
<th>Focal-Onset Seizures</th>
<th>Primary Generalized Seizures</th>
<th>Lennox-Gastaut Syndrome</th>
<th>Infantile Spasms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tonic Clonic</td>
<td>Absence</td>
<td>Myoclonic</td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>+</td>
<td>+</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>+</td>
<td>+</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Primidone</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>?</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Sodium valproate</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Clobazam</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>+</td>
<td>?+</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>+</td>
<td>?+</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Topiramate</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>+</td>
<td>?</td>
<td>↓</td>
<td>?</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
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<td>+</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>+</td>
<td>+</td>
<td>?+</td>
<td>+</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>+</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Stiripentol</td>
<td>+</td>
<td>+</td>
<td>?+</td>
<td>+</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>+</td>
<td>?+</td>
<td>?+</td>
<td>?+</td>
</tr>
<tr>
<td>Rufinamide</td>
<td>+</td>
<td>+</td>
<td>?+</td>
<td>+</td>
</tr>
<tr>
<td>Lacosamide</td>
<td>+</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Brivaracetam</td>
<td>+</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

* Lamotrigine may worsen myoclonic seizures in some patients.

The treatment of epilepsy with AEDs is known to influence sleep structure. There is strong evidence suggesting that barbiturates, benzodiazepines (BDZ) and – to a lesser degree – phenytoin (PHT) have detrimental effects on sleep. These drugs induce sleep more easily and increase total sleep time but, in contrast, reduce REM sleep. Sleep may therefore be impaired
overall and may lead, at least in part, to EDS which is often seen in people taking these AEDs. On the other hand, GBP, LEV and LTG probably have a positive effect on sleep structure resulting in more REM and SWS (N3). Thus the newer generation AEDs may have fewer detrimental effects on sleep structure than the older ones. It is, however, very difficult to measure the direct effects of AEDs on sleep because of the many confounding factors (seizures, concurrent sleep disturbances and polypharmacy) (1).

8. Influence of AED on sleep in patients with (drug resistant) epilepsy

Patients with epilepsy are already per se on a higher risk of developing a sleep disorder, as mentioned above. In addition to nocturnal seizures, poor seizure control, comorbid affective disorder can even worsen their sleep quality and QoL. In this context we have to choose the antiepileptic therapy wisely to avoid additional potentially sleep disturbing side effects. Several commonly used AEDs are known to influence sleep quality and architecture. Although these AEDs are only partly responsible for sleep cycle disturbance in epilepsy patients, an understanding of their impact on sleep can help clinicians preventing unnecessary worsening of sleep quality. Important factors concerning AEDs affecting sleep are the rate of AED dose escalation and the duration of AED therapy. Furthermore, newer generation generally tend to cause less disturbance of the normal sleep architecture (16). In addition, prolongation of REM sleep and improved sleep efficiency are potential benefits of some newer AEDs that may secondarily contribute to suppression of seizures and decreased epileptogenicity (16). Some AEDs may also be useful in the treatment of several sleep disorders. For example, GBP, carbamazepine (CBZ) and LTG may have positive effects on RLS (51). The influence of circadian rhythms on epileptogenicity is a concept that has been revisited in recent years (16). A more profound understanding of the relationship between biological rhythmicity throughout the 24-hour awake-sleep cycle and the propensity to have epileptic seizures at particular times within the cycle will allow more directed application of timed AED therapy (16).

As mentioned in the introduction, sleep is typically divided into REM and NREM phases. The distinction between these phases is based on the parameters of EEG, respiration, eye movement and EMG. The NREM phase consists of the light stages of sleep (N1 and N2), followed by a deep SWS (N3). Sleep disturbance is persistently ranked among the top 3 side effects in epilepsy patients (16). A study of de Weerd et al. in 2004 investigated whether sleep disturbances are more frequent among patients with partial seizures compared to controls and
evaluated what impact on QoL sleep disturbance may have in these patients. The authors observed that sleep disturbance was more than twice as prevalent in the epilepsy patients (39% versus 18% in the control group) and that most domains of sleep were significantly disturbed. People with epilepsy already tend to have a significant reduction in QoL, being reinforced by this sleep disturbance (2). In 2011, de Weerd conducted another study, in cooperation with Van Golde et al., focusing on prevalence, impact on QoL and effects of treatment of sleep disorders on the course of epilepsy. Concerning the prevalence, a large difference between epilepsy patients and the control group was observed in measures of EDS (13.8%) and psychiatric sleep disorders (14.1%). In other questionnaire-based studies, sleep complaints reported by adult epilepsy patients varied from 16.9% to 36% (1).

NREM sleep, as well as its deficit, are thought to promote epileptiform discharges, with a more thorough effect on diffuse discharges. Contrary, during REM sleep, the topology, distribution and frequency of epileptiform discharges are reduced (52). Several authors explain this inhibition of epileptiform activity during REM sleep by desynchronization of cerebral networks, whereas the facilitation of this activity during NREM sleep could be the consequence of an increased synchronization of the EEG pattern (1).

Sleep efficiency is defined as the time spent asleep divided by the time spent awake during a given sleep period. In subjects with a normal sleep, this value should be 85-90% (16). As explained in the introduction, epilepsy patients often show sleep fragmentation, meaning frequently arousals as well as changes in the amount of time spent in a particular sleep stage, independent of nocturnal seizures or AED use (53). Moreover, Placidi et al. noticed in 2000 that frequent phase shifts increase frequency of seizures and IED (54). On the other hand, both daytime and nocturnal complex partial seizures tend to fragment sleep due to frequent awakenings, an increase in the amount of stage shifts, a decrease in REM-sleep duration and SWS and a prolonged sleep onset and REM latency (55-57).

Daytime somnolence or drowsiness seems to occur more within the use of older AEDs, with an even greater incidence of somnolence in patients on polydrugtherapy (58). An extra factor predisposing to a greater risk of developing a decreased daytime vigilance, is rapid escalation of daily dozing off. In general, tolerance develops shortly after therapy initiation. Although, some patients report a persistent drowsiness that occasionally may lead to a poor compliance or discontinuation of the prescribed AED.
Insomnia is defined by DSM-IV as the difficulty of initiating or maintaining sleep, non-restorative sleep and significant impairment in daytime functioning during at least one month. It is characterized by the following criteria - sleep latency of more than 30 minutes, sleep efficiency if less than 85% and sleep disturbance occurring >3 times per week (59). In the overall population, the prevalence of chronic or severe insomnia has been estimated around 10% (60). In 2013, Vendrame et al. evaluated 152 patients diagnosed with epilepsy based on a questionnaire survey. The prevalence of moderate and severe insomnia amounted to 51% in these patients, with a stronger association in patients taking higher numbers of AEDs and coexisting depressive symptoms. Insomnia, as well as sleep quality, were significant predictors of a decreased QoL. Surprisingly, insomnia seemed not to correlate with worse seizure control. It is important to mention the following limitation of the study: there was no control for the presence of undiagnosed sleep apnea (61). Other investigators documented comparable insomnia rates (50% and 52%) in adult epilepsy patients (1). Reported rates of insomnia in epilepsy patients for specific AEDs are 2.2% (CBZ), 4.9% to 6.4% (LTG), 4.2% to 6.3% (LEV), 5% (PGB), 2.3% (TPM), 3.4% (VPA) and 6.6% (VGB) (62).

9. Overview most commonly used AEDs and their effect on sleep in epilepsy patients

9.1. Benzodiazepines (BDZ)

BDZ act by increasing neuronal inhibition by binding to GABA\textsubscript{A} chloride channels. GABA is the most common neurotransmitter in the CNS, found in high concentrations in the cortex and limbic system. GABA is an inhibitory neurotransmitter and thus reduces the excitability of neurons. GABA produces a calming effect on the brain. Besides epilepsy, BZD are prescribed for many other indications, including insomnia. The effects of BDZ on nocturnal sleep in epilepsy have been reported as followed: enhanced sleep-onset latency, increased length of the light stages of sleep, decreased SWS, prolonged REM-sleep latency and reduced overall REM-sleep duration (54). Furthermore, chronic BZD therapy results in a significant decrease in number of arousals after falling asleep. Piedad et al. also describe an unfavourable subjective daytime somnolence reported by 25% to 33.3% of epilepsy patients receiving diazepam (62). Some BDZ (as estazolam and temazepam) are known to reduce N3 (SWS) (63). N3 is known as the stage with the highest arousal threshold. While BDZ decrease N3, they paradoxically increase arousal threshold. Given the known action of these drugs on the
cortex, it is important to question whether these declines represent a drug effect directly affecting N3 or if they show the reduced ability of the cortex to produce high amplitude slow waves, which is the surrogate measure of N3 (63).

### 9.2. Phenobarbital (PBT)

Similarly to BZD, PBT binds to the GABA<sub>A</sub> receptor, increasing the influx of chloride ions. Therefore, it’s not surprising that analogous effects to BZD on sleep are described: PBT also reduces the number of awakenings and sleep latency and diminishes REM phase duration (54).

### 9.3. Ethosuximide (ETX)

ETX exhibits its antiepileptic effect by selectively inhibiting T-type calcium channels in thalamic neurons. Cited by Placidi et al., it has been reported that ETX increases REM sleep phase, reduces SWS, enhances the light stages of sleep and increases the number of awakenings after sleep onset (54, 56).

### 9.4. Phenytoin (PHT)

PHT acts by inhibiting voltage-gated use-dependent sodium channels. Piedad et al. reported subjective somnolence, sedation or sleep disturbance in 23.1% of epilepsy patients receiving PHT treatment (62). The acute effects of PHT consist of a decrease in sleep-onset latency and of the light stages of sleep (N1 and N2) with an accessory increase in SWS. Contrary, chronic use of PHT leads to an increase in the duration of light stages and a decrease in SWS. Furthermore, PHT leads to a reduction in sleep efficiency and a shortening of the REM phase (54). Lastly, PHT is also thought to multiply the number of arousals (64).

### 9.5. Carbamazepine (CBZ)

CBZ acts antiepileptic by inhibiting voltage-gated sodium channels. Piedad et al. describe subjective somnolence in 22% to 32.3% of epilepsy patients with CBZ treatment (62). In 1997, Gigli et al., compared subjective and objective daytime somnolence indicators in newly-diagnosed temporal lobe epilepsy patients with results from healthy participants. Both groups received 400mg CBZ twice a day during one month. PSG was conducted in order to assess changes in sleep architecture. The initial administration of CBZ seemed to lead to an increase in the number of sleep stage shifts, a reduction of REM sleep, increased fragmentation of REM sleep and a significant decrease in sleep latency. These effects on sleep architecture were reversed after one month, with values not significantly different from
baseline measures (16). More recently, in 2011, Cho et al. evaluated 15 patients with partial epilepsy on 400mg/day of CBZ. They observed an increase in SWS duration and sleep efficiency (65).

9.6. Valproic Acid (VPA)

VPA has three major molecular effects: it inhibits GABA degradation, blocks voltage-gated sodium channels and reduces calcium currents. Piedad et al. described a subjective somnolence reported by 2.3% to 45% of epilepsy patients using VPA. There is no consensus yet about the exact effects of VPA on sleep architecture (62). Early studies reported no influence on sleep architecture with stabilization of the sleep cycles. More recent investigations suggest that VPA increases the number of arousals and elongates SWS (14). VPA is also thought to prolong N1 (64). Lastly, it would decrease the length of the REM phase (54).

9.7. Felbamate (FBM)

FBM is an anticonvulsant drug with dual actions on excitatory (N-methyl-D-aspartate (NMDA)) and on inhibitory (GABA) brain mechanisms. It inhibits NMDA responses by a channel blocking mechanism and potentiates GABA responses (66). Placidi et al. reported in 2000, insomnia precipitated by acute as well as by chronic FBM therapy (54). In 2008, Grosso et al. evaluated efficacy and safety of FBM in 53 children under the age of four. 13% of them reported somnolence and an additional 9% had unspecified sleep disturbance complaints (67).

9.8. Lamotrigine (LTG)

The primary antiepileptic effects of LTG are thought to include inhibition of presynaptic voltage-sensitive sodium channels and impairment of glutamate release (68). One of the most common side effects of LTG is a dose dependent drowsiness. Hirsch et al. linked drowsiness to psychomotor slowing, fatigue or lethargy. 5.7% of the patients participating to the study of Hirsch et al. reported a drowsiness so severe that dose change was required. The authors also describe a non-dose dependent insomnia in 1.1% of the patients leading to a dose adaptation (69). In 2001, Foldvary et al. evaluated the influence of add-on LTG on sleep perception, sleep architecture and daytime alertness. The study subjects were 10 epilepsy patients taking either PHT or CBZ. PSG showed a statistically significant increase in N2 sleep stage and a decrease in N3 sleep stage. Moreover, an increase in REM sleep duration was observed, but seemed to be not statistically significant. Furthermore, the majority of the subjects mentioned
decreased sleep latency and improved consolidation of nocturnal sleep (55). Placidi et al. conducted PSG in 13 drug resistant epilepsy patients on LTG treatment. This investigation resulted in a significant prolongation of REM sleep and a non-significant decrease in N3 sleep stage.

9.9. Levetiracetam (LEV)

The antiepileptic effects of LEV are mediated by binding to SV2A, a transmembrane protein that plays a role in calcium-dependent presynaptic neurotransmitter release (70). In a clinical trial of Shorvon et al., conducted in 2000, following observations concerning somnolence in epilepsy patients taking LEV were made: 9.4% of patients receiving 1000mg/day as add-on therapy reported this side-effect and 11.3% of patients receiving 2000mg/day (both findings compared to 4.4% in the placebo group) (71). Furthermore, Ben-Menachem et al. investigated the effect of 3000mg/day as add-on and stated somnolence in 6.1% of patients (compared to 3.8% in the placebo group) (72). Also in 2000, Cereghino et al. performed another trial in order to evaluate the effect of LEV on daytime sleepiness. The authors reported that 20.4% of patients taking 1000mg/day and 18.8% of patients receiving 3000mg/day mentioned to suffer from daytime sleepiness (compared to 13.7% in the placebo group) (73). In 2006, Tsai et al. followed 47 Taiwanese epilepsy patients in order to investigate the efficacy and safety of LEV treatment. 40.4% of patients in the experimental group (versus 14.9% in the placebo group) reported somnolence, consequently being the most commonly mentioned adverse effect. Nuancing this seemingly big number, >80% of the reporting instances described this somnolence as only being ‘mild’. Furthermore, this number differs noticeably from the numbers reported of the two previously mentioned studies. This could be explained by the greater degree of concomitant AED therapy reported in these two studies (74). Still in 2006, Cicolin et al. exerted PSG’s and MSLT in 14 healthy volunteers receiving ≤2000mg/day of LEV. The authors observed a relative decrease in time spent in REM sleep and a significant increase in time spent in all REM stages. In general, LEV showed to be predisposed for sleep consolidation, without having negative effects on daytime vigilance (75). In an earlier study in 2002, performed by Bell et al., 16 patients with a history of partial epilepsy treated with stable CBZ monotherapy and 12 volunteers were followed. Both groups received a single dose of 1000mg of LEV or placebo. The investigation led to following observations: in the patient group only, an increase in total time spent in stages N2 and N3 of sleep was seen. In the volunteer group only, prolongation of REM latency was observed. The epilepsy patients
pretended having a more restful sleep while volunteers said to be less alert and groggier on awakening (76).

### 9.10. Zonisamide (ZNS)

The antiepileptic effects of ZNS are mediated through several molecular mechanisms: antagonism of voltage-dependent T-type calcium channels, inhibition of voltage-sensitive sodium channels, glutamate blockade, induction of GABA release and inhibition of carbonic anhydrase. In 2005, Brodie et al. randomized 351 patients into 4 groups. Three groups received an adjunctive seizure treatment of ZNS at escalating doses. Results of these patients were compared to a fourth group of patients, receiving a placebo treatment. The report of somnolence varied according to the dose of ZNS: within the 100mg/day dosing group, 5.4% of patients reported somnolence; compared to 3.6% within the 300mg/day group and 14.4% within the 500mg/day group (77). In 2013, Romigi et al. monitored 12 patients with localization related epilepsy in order to investigate the effects of ZNS on nocturnal sleep and daytime vigilance. Patients were evaluated prior to and following 3 months of ZNS treatment, based on four measures: PSG, MSLT, the Pittsburgh Sleep Latency Index (PSQI) and the ESS. No statistical significance for any of those measures was assessed after completion of the monitoring period (52).

### 9.11. Topiramate (TPM)

The antiepileptic effects of TPM are mainly mediated by four mechanisms: GABA-facilitated inhibition, blockage of voltage-dependent sodium channels, modulation of voltage-dependent calcium channels and antagonism of AMPA receptors (54, 56, 68). Somnolence was reported more frequently in trials where TPM was given as add-on therapy (16), when compared to gradual titration in monotherapy trials (78). In 2000, Reife et al. conducted a double-blind, placebo-controlled trial where TPM was given as an adjunctive therapy to 743 adult subjects diagnosed with localization-related epilepsy. 30% of patients receiving 200-400mg/day and 28% of patients taking 600-1000mg/day reported somnolence. About 90% of patients mentioned this adverse effect and rated the severity as mild or moderate. Furthermore, the majority of these adverse events occurred shortly after TPM therapy initiation and disappeared with continued treatment. The most prevalent reason to stop TPM treatment was daytime sleepiness, accounting for 3.2% of all discontinuations. Rapid titration was one of the predisposing elements for the development of negative side effects (79). In 1999, Glauser summarized data from six clinical trials about TPM: somnolence was reported by 26.7%,
26.5%, 16.9%, 19.7% and 27.7% of the patients at respective doses of 200, 400, 600, 800 and 1000 mg/day. In trials where TPM was given as monotherapy, somnolence was only reported in 13% of the patients, whereas, in trials with adjunctive use of TPM, somnolence was reported in 29% of the subjects (16). In the patients with a diagnosis of localization-related epilepsy, receiving 50mg/day or 500mg/day of TPM, somnolence was reported in 14% (16, 80). An Italian study, conducted by Bonanni et al. in 2004, followed 14 newly diagnosed localization-related epilepsy patients, who did not get any pharmacological treatment beforehand, after initiation and titration of up to 200mg daily dose of TPM monotherapy for a 15-week period. Daytime sleepiness was assessed with the ESS and the MSLT. Besides this, psychomotor performance was evaluated, based on simple and choice visual reaction times. When compared to similar measures in control subjects, patients within the treatment group demonstrated no statistical variation in daytime vigilance profile or psychomotor performance (81). Lastly, sleep latency in epilepsy patients may be shortened by the use of TPM (64).

9.12. Gabapentin (GBP)

GBP is an amino acid and structural analogue of GABA. The antiepileptic effects of this AED are secondary to glutamate synthesis modulation and inhibition of voltage-sensitive calcium channels (54, 56). Subjective somnolence had been reported by 12.1% of epilepsy patients taking GBP in the study of Piedad et al (62). In 2002, Foldvary-Schaefer et al. conducted a study with 10 healthy adults in order to evaluate the effect of 1800 mg/day of GBP on sleep architecture and daytime vigilance. The authors reported an increase in baseline SWS in the treatment group but this was not statistically significant when compared to the control group (55). In 2000, Placidi et al. evaluated 10 patients suffering partial epilepsy after 3 months receiving 1800mg GBP a day. In all 10 patients, PSG was executed and showed an overall significantly increase of REM sleep percentage, a prolonged REM duration, a reduced number of awakenings and a decreased length of the N1 sleep stage (54). Simultaneously, Placidi et al. conducted another, independent study in which 18 patients diagnosed with drug resistant partial seizures undergoing a 4-month lasting treatment with 1800 to 2400 mg/day of GBP. The authors reported a significant increase in REM and SWS percentage, a diminishment in the number of awakenings and a decrease in the duration of N1. Improvement of sleep quality was reported by 16 patients. EEG recording showed no significant changes in frequency of IED’s (82).
9.13. **Pregabalin (PGB)**

PGB binds to voltage-gated calcium channels in the CNS, showing analgesic, antiepileptic and anxiolytic effects. In 2005 Beydoun et al. somnolence in 30.1% of epilepsy patients taking 600mg/day, divided into 2 doses, versus 12.2% of volunteers in the placebo group. When 600mg/day was divided into 3 doses, 23.4% experienced somnolence (83). According to two studies, performed by respectively French et al. in 2003 and Arroyo et al. in 2004, 6.1% to 17.4% of patients receiving 150 mg/day reported this side effect (84, 85). Within the first 2 weeks of the start of the therapy somnolence seemed to be mild or moderate in intensity (86). In 2005, 24 healthy subjects received PGB and the following observations were made: an increase of time spent in SWS, a decrease of the number of awakenings, an augmented total sleep time, a reduced sleep-onset latency and improved sleep efficiency (87). Two years later, a randomized placebo-controlled study was performed by Haas et al.. In 17 patients with well-conducted partial seizures, PSG and subjective sleep questionnaires were utilized in order to evaluate the effects of 300mg/day of PGB. A subjective improvement in the number of awakenings was reported but this could not be revealed as statistically significant when analysed with PSG (88). In 2009, 12 patients with a history of drug resistant seizures were evaluated twice with PSG and based on the ESS. The evaluation occurred by Romigi et al., before and after a 3-month lasting complementary therapy with PGB. Two significant findings were reported: an increase in the REM phase and decrease in N2 sleep percentage (89).


TGB increases concentrations of GABA by inhibiting reuptake of the neurotransmitter (66). Piedad et al. note that TGB increases the duration of SWS and they report subjective somnolence in 1.1% of epilepsy patients (62).

9.15. **Vigabatrin (VGB)**

VGB inhibits GABA transaminase facilitated GABA uptake, increasing concentrations of the neurotransmitter (66). Piedad et al. reported subjective somnolence in 11.3% to 25.7% of patients with epilepsy on VGB therapy (62). In a study conducted by Placidi et al. in 2000, no changes in PSG and daytime somnolence were observed when VGB was given as add-on therapy to a group of epilepsy patients (56). In an earlier study by Siegel et al. in 1998, 3 epilepsy patients with VGB use showed prolongation of REM sleep latency (16).
9.16. **Lacosamide (LCM)**

The main antiepileptic effect of LCM consists of a selective slow inactivation of voltage-gated sodium channels (90). Piedad et al. reported a subjective somnolence of 5.1% (for the IV formulation) to 9.1% of epilepsy patients on LCM treatment (62).

9.17. **Oxcarbazepine (OXC)**

OXC exhibits its antiepileptic effect mainly by inhibiting of voltage-sensitive sodium and calcium channels (66). According to Piedad et al., 15.7% of epilepsy patients receiving OXC reported subjective somnolence (62).

9.18. **Perampanel (PPN)**

PPN is thought to exert its antiepileptic effect via a non-competitive antagonism of the AMPA type glutamate receptor (91). Three studies performed by respectively French et al., Krauss et al. and Rektor et al., all conducted in 2012, evaluated the effect of PPN on subjective somnolence. These studies showed that subjective somnolence varies along the administered dose regimen. 12.2% of patients receiving 2mg/day reported this side-effect, 5.9% to 20% in patients on 4mg/day and 12.4% to 26.7% of patients on 12 mg/day (92-97).

10. **Effects of VNS on respiration during sleep in drug resistant epilepsy patients**

A study conducted by Hallbook T. et al. has shown a significant reduction of sleep-latency after 9 months VNS treatment. Furthermore, they have reported an increase of N3 and a decrease of N1 sleep. However, not only beneficial effects on sleep are reported in patients treated with VNS. For example, Prazighar F. et al have noted an increase of the apnea/hypopnea index (AHI) in epilepsy patients treated with VNS (98). Defined by the American Academy of Sleep Medicine (AASM) an obstructive apnea or hypopnea can be defined as an event that lasts for ≥ 10 s and is characterized by an absence or a decrease from baseline in the amplitude of a valid measure of breathing during sleep, that either reaches >50% with an oxygen of 3% or an arousal (alternatively a 30% reduction with 4% desaturation) (99). The AHI is the combined average number of apneas and hypopneas that occur per hour of sleep. According to the American Academy of Sleep Medicine (AASM) it is categorized into mild (5-15 events/hour), moderate (15-30 events/hour) and severe (>30 events/hour) (100). So, <5 events per hour of sleep, is still regarded as ‘normal’. This is an important finding, knowing that epilepsy patients already have a higher risk of developing respiratory sleeping disorders, reported in Malow et al. (24).
Several studies have shown the association of VNS and respiratory symptoms such as dyspnea, laryngeal irritation and hoarseness. During a study of Malow et al., conducted in 2000, the effects of VNS on sleep-related breathing have been investigated. Therefore, 4 epilepsy (one already diagnosed with OSAS) patients underwent PSG before and after 3 months of VNS treatment. Two of the 4 patients also underwent follow-up PSG to assess the effects of changing stimulus parameters on sleep-related breathing. All 4 patients showed consistent sleep-related decreases in airflow and effort coinciding with VNS activation, but most events did not meet laboratory criteria for apneas or hypopneas. For those airflow decreases that did comply with the definition of apnea and hypopnea, VNS also induced a higher rate of these hypopneas and apneas during activation, compared to a non-activational status. In all 4 patients, AHI during VNS activation exceeded 10 apneas and hypopneas per hour. Although, in the 3 patients not suffering from OSAS, the average AHI for the entire night (combination of periods of VNS activation and non-activation) was less than 5 apneas and hypopneas/hour. In one patient with OSAS before VNS treatment, AHI rose from 4 (pretreatment) to 11.3 (treatment) (101).

Both CNS and peripheral nervous system (PNS) mechanisms offer plausible explanations for these decreases in airflow and respiratory excursion (the degree in which the thorax ribcage expands and contracts whilst breathing) induced by VNS. The stimulation effects include CNS mechanisms by influencing central projections to the reticular formation of the medulla (mPRF). Non-respiratory, ACh mPRF receptors contain efferent and afferent connections to the pontomedullary nuclei, which are known to regulate breathing and the upper airway musculature of the larynx and pharynx. So when ACh agonists are injected into the mPRF, frequency of breathing, tidal volume and minute ventilation alter (101). Concerning the PNS, stimulation of VN afferents may activate motor efferents whose cell bodies originate in the dorsal motor nucleus of the VN and in the nucleus ambiguous. Activation of these efferents alters neuromuscular transmission to the upper airway muscles to produce upper airway narrowing (101). Respiration may also be influenced by VNS through effects on sleep architecture.

As mentioned above, 2 of the 4 patients underwent follow-up studies during which stimulation parameters were changed in order to evaluate their individual effect on hypopneas
and apneas. One of the patients had pre-existing OSAS, the other patients did not. To guarantee that conditions were sampled for an adequate amount of time, the studies were limited to reducing only a few combinations of parameters. The parameters were initially set as follows: intensity at 1.5 mA, frequency at 30 Hz, on/off – time at 30s/5min and pulse width at 500 µs (101).

In the patient with preexisting OSAS, several apneas and hypopneas were registered with these initial settings. Secondly, on-time was reduced to 7.5 s, with off-time and all other parameters constant. This seemed to have no effect: the decreased airflow and effort during VNS activation persisted for the length of the stimulus. Thirdly, pulse width was reduced to 125 µs (with all other parameters set following the initial settings). The apneas and hypopneas also persisted by reducing this parameter. As fourth, stimulus frequency was reduced to 20 Hz (with other parameters constant) and during 2 consecutive activations, no hypopneas and apneas were present, only a mild decrease in airflow and effort was observed. When frequency was reduced to 10 Hz, the decrease in airflow and effort was minimal. The investigators took into account that a supine sleeping position affects breathing by effects of gravity. They also kept in mind that REM sleep causes a decrease in muscle tone on the upper airway. Therefore, 1 hour of supine sleep and samples of REM sleep were obtained at each frequency. Lastly, stimulus intensity was reduced in steps of 0.25 mA to a minimum of 0.5 mA (with other parameters constant). Apneas and hypopneas seemed to persist at all stimulus intensities (101).

In the patient without OSAS, as in the patient with OSAS, reductions in stimulus frequency ameliorated VNS-related respiratory events. Also similar to the findings in the patient with OSAS, concerned the statement that reductions in pulse width and on-time had no significant effect. On the other hand, in contrast to the patient with OSAS, a stimulus intensity reduction to 1.25 mA resulted in only a mild decrease in airflow and effort. Apneas and hypopneas did persist at intensities of 1.75 mA and 1.5 mA (101).

The remarkable effect of VNS frequency can be explained by its important functional repercussion on several mechanisms, including vocal cord movement. According to two different studies exerted by Zumsteg et al. in 2000 and by Lundy et al. in 1993, this movement seems to be frequency-dependent during VNS. Zumsteg et al. evaluated vocal cord movement during stimulation in 3 epilepsy patients by fiberoptic laryngoscopy. In all 3 patients left vocal fold adduction and laryngeal torsion was stated with a VNS frequency of
30 Hz (with other parameters set following previous controlled studies where these specific values have been shown to be effective and well tolerated (0.25 to 2 mA intensity, 500 µs pulse-width and an on/off-time of 30s/5 min)). In the study by Lundy VNS frequencies of 40Hz and higher also led to left vocal fold adduction and laryngeal torsion. In contrast, frequencies of 20 Hz resulted in left vocal abduction. During this study, other stimulus settings were used than in the Zumsteg et al. study: stimulus intensity was 3 mA and duration was defined as 3 ms (pulse width was not specified) (101).

The mechanism(s) by which VNS frequency influences vocal cord position and sleep-related breathing is not exactly known. It is known that increased frequency of nerve traffic releases higher amounts of neurotransmitters and recruits more motor postsynaptic elements. However, the exact parameters regulating this enhanced recruitment are complex and include cell size, membrane time-constant, input resistance and conductance properties (101).

As mentioned above, in patients without predisposition to OSAS, the VNS-induced respiratory changes may not be clinically important. In contrast, in 2003 Holmes et al. presented a case of a 21-year old female epilepsy patient who manifested symptoms consistent with sleep apnea and who had an increased AHI after VNS placement in 1999. These led to self-reported EDS and subjective sleep disruption. Daytime sleepiness became more apparent when VNS stimulus intensity was increased to 3.5 mA due to a high seizure frequency. At insistent request of the patient, VNS was discontinued after PSG, resulting in a complete resolution of daytime sleepiness (102).

11. VNS reduces daytime sleepiness in drug resistant non-OSAS epilepsy patients
As mentioned in the introduction, VNS affects two key regulatory systems involved in facilitating wakefulness: the ACh and the NOR system. Given the connections of brainstem regions involved in these systems to the PBN and the role of these regions in promoting alertness, Malow et al. postulated in 2001 that VNS may decrease daytime sleepiness in humans. In order to test this hypothesis, results of PSG, MSLT and ESS scores in 16 subjects with drug resistant epilepsy were compared before and after 3 months VNS treatment. To address the concern that most sleep disorders cause daytime sleepiness and influence REM sleep, adults with an AHI >10 per hour on their baseline PSG, as well as subjects suffering any other sleep disorder than OSAS were excluded. Over 80% of the patients were maintained on constant doses of AEDs by the referring physicians. VNS parameters were titrated to seizure frequency and subject tolerance. Before initial programming and activation
of VNS, each of the 16 adults underwent baseline PSG followed the next day by a MSLT to evaluate daytime sleepiness. Furthermore, the number of naps in which REM sleep occurred, was also recorded. Non-epilepsy adults have a sleep latency average of ten minutes or more and seldom show REM sleep during naps. Fifteen study subjects completed baseline and treatment MSLT. In order to avoid bias, subjects were told that the objective of the study was to investigate the effects of VNS on overnight sleep and on a daytime nap. They were not informed about the fact that they may experience an increase in time to fall asleep during their daytime nap test. (26).

Suggesting a reduction in daytime sleepiness, the MSL increased from an average of 6.4 minutes to 9.8 minutes. However, this should be interpreted with caution, given the fact that further examination revealed possible effect of stimulus intensity. Twelve subjects with VNS intensity ≤1.5 mA had higher MSL and were less sleepy after treatment as compared to the baseline tests. On the other hand, all 3 adults receiving intensities >1.5 mA, had lower MSL as compared to baseline MSL. However, 2 of them had seizures preceding the treatment MSLT and poor sleep efficiencies on their treatment (compared to baseline MSLT). Those two elements may have affected the MSLT results, so it is difficult to make an unequivocal statement concerning the influence of VNS intensity. Seven out of 9 subjects with no reductions in seizure frequency, showed improvement on MSLT scores, indicating that MSLT scores are not correlated with reduction in seizure frequency.

Daytime naps in which SOREM periods occurred, were established in 9 of the 61 treatment naps and in 2 of the 61 baseline naps. The occurrence of REM sleep during naps has been documented in narcolepsy and other conditions, such as OSAS, which may contribute to daytime sleepiness. Contradictorily, 3 of the subjects with REM sleep periods during daytime naps were less sleepy during the day when treated with VNS (compared to their baseline MSLT results). This remarkable discrepancy between clinical sleepiness and manifestations of SOREM episodes, suggests that VNS may simultaneously activate regions that promote REM sleep and regions that enhance alertness (26). This presumption is supported by the previously reviewed neuroanatomic connections. REM sleep and wakefulness are states of relative cortical activation promoting alertness and mainly suppress IEA and several types of epileptic seizures. This in contrast to NREM sleep, a stage of relative neuronal desynchronization, that as mentioned before, promotes spike-wave discharges. NREM sleep also enhances IEA and seizures in most epilepsy syndromes. Therefore, the antiepileptic
effects of VNS are likely to be mediated via stimulation of neurochemical systems that modulate cortical activation and promote REM sleep and alertness (26).

All of the 16 subjects completed a baseline and a treatment ESS. The mean score decreased from 7.2 to 5.6. Similarly to the MSLT results, an effect of stimulus intensity was noted. Indicating increased or unchanged subjective daytime sleepiness, all 3 patients with VNS stimulus intensities >1.5 mA showed higher or unchanged ESS scores. Nine out of the 13 subjects with stimulus intensities ≤1.5 mA had lower ESS scores, suggesting improved daytime sleepiness. Also comparable to the MSLT, 5 out of 9 subjects without seizure frequency reduction showed an ameliorated ESS score, indicating that there is no correlation between both parameters. The authors included the ESS in order to complement the MSLT results with non-physiologic or behavioral measures. Although changes in ESS scores with treatment were consistent with those of MSLT results (e.g. the effect of stimulus intensity), the ESS and the MSLT changes in treatment were not correlated. This finding corresponds to results of previously conducted studies comparing the ESS and the MSL in patients with OSAS (103), or EDS due to OSAS or other conditions (104), which also failed to demonstrate an interrelationship. A possible explanation for this dissociation, could be that people who are chronically sleepy habituate to their symptoms and may not be aware of the extent of their daytime sleepiness (26).

PSG overnight recordings included EEG, EOG, submental EMG, nasal-oral airflow, respiratory effort, pulse oxymetry, anterior tibialis EMG and VNS signal. Studies were scored by a qualified PSG technologist who was not informed about the study condition (baseline or treatment). For the 13 subjects receiving stimulus intensities ≤1.5 mA, sleep efficiency (time asleep/time in bed) did not change and no changes were observed in sleep architecture. This is in contrast to the changes in REM sleep on daytime MSLT. In 2 of the 3 patients treated with intensity >1.5 mA, sleep efficiency on treatment was notably decreased compared to baseline PSG. Reductions of relatively 80% to 27.3% and 82% to 37% were established (26). No plausible explanations for these decreases were found.

It is important to mention that we cannot exclude non-specific effects of VNS as physical sensations as choking and throat parasthesias. These sensations may lead to prolongation of sleep latency time and nighttime awakenings, affecting MSLT results. Therefore, the authors analysed subjective responses of the patients before and after VNS treatment. In overall, no changes in sleep latency were noted and subjects reported fewer awakenings after VNS treatment. This latter finding suggests that arousals and awakenings in these subjects were not
associated with the VNS stimulus. Although, it is important to take into account the possibility that VNS may have affected sleep maintenance (staying asleep after falling asleep) in a way which is not detectable by macro-structural analysis of the EEG (26).

As reported above, VNS treatment may affect respiration during sleep, resulting in stimulus-caused apneas and hypopneas. Despite this, the majority of the 16 subjects of this study experienced improved daytime sleepiness. This could be explained by the following two elements: the degree of sleep apnea in the subjects was not clinically significant and the improvement in daytime sleepiness due to VNS may have overshadowed possible negative effects of respiratory events on sleepiness (26).

It is difficult to avoid seizures and medication changes in an epilepsy population requiring VNS due to their high seizure frequency and to the course of the disease. As mentioned above, seizures can reduce daytime alertness and (first-generation) AEDs generally tend to cause sedation. Although the majority of the study subjects were able to remain on constant doses of AEDs for the 3-month study period, some patients did need a change in medication. The authors were uncertain that subjects in whom seizures occurred during PSG or MSLT or in whom medication changes were performed, provided data representative of the subjects as a whole. In order to eliminate these potential limitation of the study, Malow et al. reanalysed their PSG, MLST and ESS datasets removing these subjects and found comparable results to all the 16 patients combined (26).

The 16 adults showed, based on questionnaire data before and after 3-months VNS, an average decline in seizure frequency of 25% (with only 25% obtaining a reduction of ≥50%). After 7 to 20 months of follow up, the mean reduction in seizure frequency augmented to 57% (with 69% achieving a reduction of ≥50%). These findings correspond to the long-term efficacy of VNS which has been reported on multiple occasions in the past. This improvement in seizure frequency may be, as previously mentioned, due to (a combination of) modification of stimulus parameters or/and to a cumulative effect of VNS over time (26).

12. Effects of chronic VNS on sleep structure
In 2004 Rizzo et al. evaluated the repercussion of chronic VNS on sleep background EEG and interictal epileptiform activity (IEA) (described as isolated spikes and discharges), in patients with drug resistant epilepsy. Confirming earlier reported data on the effect of acute VNS on
human EEG in a state of wakefulness, results of this study showed that acute VNS has no direct effect on wake, neither on sleep EEG. No significant changes in the EEG composition have been observed comparing a prestimulus onset time span to the stimulus time span (34).

Concerning the long-term impact of VNS on daytime EEG in humans, a study performed by Koo et al. in 2001, revealed clustering of epileptiform activity with progressively extended periods of spike-free intermissions during wakefulness (105). In 2004, Rizzo et al. were the first to evaluate the effect of chronic VNS on sleep EEG.

Rizzo et al. included 10 adult subjects with the diagnosis of drug resistant epilepsy. Four of these subjects were excluded due to severe EEG abnormalities, resulting from a previous encephalopathy. None of the subjects included reported a history of sleep disorders, all of them said to habitually take daytime naps. The 6 subjects underwent baseline and treatment PSG, spectral analysis and IEA count. The results were compared by means of a statistical analysis (an paired t-test, independently for each evaluated variable) (34).

The baseline PSG (conducted before the VNS implantation) as well as the treatment PSG (13.7 ±3.8 months after implantation) were preceded by one night of adaptation. None of the patients showed OSAS, oxygen desaturation moments or PLMS during baseline recording. No epileptogenic seizures were stated during baseline or treatment PSG. When comparing baseline and treatment PSG, statistically significant differences were found. Firstly, chronic VNS seemed to increase N1 sleep, the number of awakenings and wakefulness after sleep onset (in duration as well as in percentage). On the other hand, REM sleep was decreased (in duration, percentage and number of episodes) (34).

In order to evaluate the sleep background EEG, a spectral analysis was conducted. A spectral analysis is a mathematical approach to quantify the EEG (106). The mean purpose of quantifying an EEG is to identify and locate maladaptive brain activity patterns that correspond to diagnostic information and/or cognitive deficits in e.g. epilepsy (107). The spectral analysis, therefore, decomposes EEG signals into their constituting frequency components. As we know, the brain waves (alpha, bèta, …) all have a specific frequency range, so due to spectral analysis, we can observe the type of brain waves in the EEG signals (also called the spectral content of the EEG) (106). The Fast Fourier Transform (FTT) is a
widely applied method in spectral analysis, that is also used in this study. However, we will not further set out the FTT method, leading us to far.

In this study, Rizzo et al. derived the EEG from channel C4-P4 because this seemed to be least affected by epileptogenic discharges. Power spectra were calculated with 0.5 Hz resolution in the frequency range 0.5–15.5 Hz, then collapsed into 5 frequency bands (low delta: 0.5–2 Hz; high delta: 2–4 Hz; thèta: 4–8 Hz; alpha: 8–12 Hz; sigma: 12–15.5 Hz) for statistical analysis purposes. Mean absolute power values of each EEG frequency band were computed for NREM sleep, REM sleep and wakefulness. EEG segments (epochs) containing artifacts, epileptogenic discharges, arousals and wakefulness after sleep onset were discharged.

When comparing the EEG total power (this is the sum of absolute (amount of power in a frequency band at a given electrode) EEG powers (6)) to the pre-treatment status with the EEG total power after 14-months of VNS treatment, Rizzo et al. observed a statistically significant overall increase in all of the 3 evaluated states (wakefulness, REM sleep and NREM sleep). This enhancement seemed to be more significant in NREM sleep than in REM sleep and wakefulness. Additionally, the frequency intervals in which significant augmentations were found, differed between NREM sleep and, REM sleep and wakefulness. During the latter two, the enhancement was mostly observed in fast activities (8-14 Hz). To be more specific: during wakefulness, alpha activity was predominantly increased; during REM sleep, thèta activity was more represented than before VNS treatment. This while in NREM sleep, the rise was mainly stated in slow activities (1-7 Hz), consisting of primarily delta and sigma rhythms. These findings can be interpreted as a reinforcement of the structural composition of EEG, which could offer a plausible explanation for the increase in total EEG power. This reinforcement, strengthened by the fact that the EEG power is augmented in all the 3 states explored, makes it highly unlikely that processes as EEG (de)synchronization are the cause for the increase in total power. Keeping in mind the lack of direct effect of single stimuli, the chronic stimulation probably produces an accumulative effect, explaining the elevation in EEG power both during sleep as well as wakefulness. This accumulation effect could induce an improvement of the cortical electogenesis and could exert an overall influence of metabolic origin on the corticothalamic EEG generating system. This latter interpretation can be partially explained from data resulting from studies investigating the effects of VNS on metabolic activity in the brain (34). These data reveal perfusion changes on Single-photon Emission Computed Tomography (SPECT) in the
corticothalamic network, resulting in an increase of perfusion on the long term. They also postulate the role of VNS in modulating and resetting altered activity of the involved structures. Finally, it should be taken into account that chronic VNS has an important impact on the quality of wakefulness, offering a different view on the interpretation of the increase in EEG power. Chronic VNS is indeed thought to empower the homeostatic drive for the sleep-wake cycle, called the ‘process S’, during the day and this could form the basis for a SWS consisting of more delta waves (34).

Regarding the IEA during sleep, the only statistically significant finding of this study confirms a diminishment of the duration of the discharges. A decrease in the incidence of IEA and an increase in the duration of spike-free intervals during sleep have also been observed, although both not significant (34).

**DISCUSSION**

AEDs have been shown to have a variety of effects on sleep and daytime vigilance. Chronic use of first-generation AEDs tend to reduce the amount of time spent in REM (observed with the use of BDZ, PHT, PBT, CBZ and VPA) and SWS (observed with the use of BDZ, PHT, PBT and ETX). SWS deprivation is known to disrupt the consolidation of explicit memories for visuo-spatial information, and both SWS and REM sleep deprivation negatively affect explicit verbal recall (108). Sleep consolidation observed with the newer generation of AEDs (mainly observed with LTG and GBP) may contribute to reduction of seizure threshold in susceptible patients by increasing REM sleep (53). This is due to the inhibiting effect of REM sleep on epileptic phenomena. Knowing that REM sleep is also involved in learning, memory processing and brain plasticity, an increase in REM sleep may improve intellectual abilities (52). However, further studies are necessary to investigate the exact effects of increased REM sleep on mental functioning.

Given the variety of sleep disorders and complaints in epilepsy patients and their significant impact on the patients’ QoL, further research should explore the potential therapeutic applications of AEDs for one or more specific sleep problem(s) observed in epilepsy. For example, based on the analysed literature, there is a need for AED clinical trials involving epilepsy patients with difficulty to maintain sleep. Therefore, AEDs that increase N3 and reinforce sleep consolidation, such as GBP, PGB and TGB could be used. Further
investigations should also be conducted for epilepsy patients with problems initiating sleep. Potential study AEDs for this population should be reducing sleep latency, e.g. PBT, PHT and CBZ. A third research area should concern therapeutic trials for epilepsy patients with insomnia. In these patients CBZ and PGB could be potential study drugs due to their positive influence on total sleep time and efficiency. At last, in epilepsy patients with EDS, avoidance of AEDs associated with daytime sleepiness such as VPA, LEV and TPM should be considered.

There are some limitations to the evaluated studies that should be taken into account. To start, knowing that epilepsy and seizures affect sleep architecture, the effects observed after adding an AED may be due to improvement in seizure control and epilepsy, rather than being a direct effect of the AED. Most of these studies had a small sample size, therefore, it was not possible to determine the effects of AEDs on sleep architecture independent of seizure control. Furthermore, some studies only compared outcomes with healthy controls (and not with baseline or placebo), so they were not able to determine the real effect of AED, independent of the effects of epilepsy. Another limitation concerns the fact that different studies for a particular AED used different doses, different evaluation methods and different study populations. Therefore, it was not possible to determine the reproducibility of the findings. Moreover, several studies used a single dose or titration dose, so it was not possible to determine whether there is a dose-response effect. Moreover, sometimes doses were adjusted based on clinical response and therefore were not uniform. Lastly, studies that used sleep assessment without any respiratory channels, were not able to rule out coexisting sleep disorders, which could also have influences sleep architecture.

Concerning the influence of VNS treatment on sleep in drug resistant epilepsy patients, we can conclude that VNS induces adverse changes in respiration during sleep. We assume that in patients without pre-existing OSAS, these VNS effects are probably not very compelling, but VNS should be used carefully in patients with pre-existing OSAS. In these latter patients, mainly stimulus frequency and on/off-time seem to have an important impact on VNS-related respiratory events. Therefore, lowering stimulus frequency or prolonging off-time may prevent exacerbation of OSAS. Of course, reduction of stimulus frequency and VNS on-time, may compromise seizure control. If this is the case or if OSAS is moderate or severe, it may
be advisable to treat OSAS. Several treatment options are available: CPAP, oral appliances, surgery, positional therapy or weight loss (101).

VNS at low stimulus intensities improves daytime sleepiness and VNS enhances daytime REM sleep. However, more studies involving larger numbers of subjects are necessary to define if high stimulus intensities negatively affect daytime sleepiness or overnight sleep in comparison to lower intensities. This potential difference could be significant by supporting the assumption that low stimulus intensities have more beneficial and less adverse effects than higher intensity. Of course this assumption is only meaningful when seizure control is also obtained with lower intensities. An example of a beneficial effect of stimulation with low intensity (0.5 mA) has been described by Clark et al. They observed that stimulation with 0.5 mA enhances memory storage as compared to higher intensities (109). Furthermore, more additional studies are also recommended to determine whether daytime sleepiness also continues to improve over time.

Moreover, the hypothesis that antiepileptic and activating effects of VNS are related, needs further investigation in experimental studies, with a specific attention to the clinical and neurophysiologic correlates affected by VNS.

It is important to mention that the patient presented by Holmes et al., who developed EDS after VNS placement, did not undergo PSG testing prior to VNS. Although, since the consistent manner in which stimulations were associated with respiratory changes and arousals, it is reasonable to assume that VNS was associated with these manifestations. Progression of her symptoms with increasing stimulus intensity was most likely related to the degree of sleep disruption.

Long-term VNS results in an enhancement in sleep EEG power of drug resistant epilepsy patients. This may be related to a better structured composition of EEG. Lastly, it is also possible that chronic VNS induces an increase in the brain’s ability to generate an electrical activity.

Concerning the possibility to predict clinical response to VNS by sleep measurements and EEG modification, several studies with small sample sizes investigated this relation. Rizzo et al. reported in 2004 that they did not find a correlation between modifications in sleep EEG composition and clinical response to VNS. The study conducted by Malow et al., showed that ameliorations in MSL and subjective daytime sleepiness during VNS treatment seemed unrelated to a decrease in the amount of seizures: 7 out of 9 subjects with no reductions in
seizure frequency, showed improvement on MSLT scores, indicating that MSLT scores are not correlated with reduction in seizure frequency. Analogously, 5 out of 9 subjects without seizure frequency reduction showed an ameliorated ESS score, indicating that there is also no correlation between both parameters.

It is very important to call into question the statistical significance of both studies, given the little sample sizes, consisting of respectively only 16 and 10 subjects. Therefore, further prospective, large sample size studies are needed to reinforce the findings of both studies.

**CONCLUSION**

Sleep problems and sleep disorders are frequently found in epilepsy patients. All currently and commonly used AEDs seem to have effects on sleep architecture. In order to optimise the management of epilepsy patients, it is important to be aware of these effects. To evaluate the effect of AEDs and VNS on sleep more in detail, more prospective studies with larger sample size and focused on dose-response relationship are strongly recommended.

When analysing studies that investigate the effect of AEDs on sleep and when comparing the results of different studies, we advice to keep following elements in mind: (I) information on previous treatments is frequently scarce and incongruent; (II) sometimes subjective measures (e.g. MSLT, ESS,…) are used and different studies may apply dissimilar methodological approaches; (III) the population groups are often diverse and different studies may conclude other types of epilepsy; (IV) different dose regimens are applied, since all AEDs have another distribution profile; (V) the duration of treatment differs; (VI) sometimes there is a failure to control for seizures; and (VII) it is difficult to control for the effects concomitant AEDs and other co-medication.

VNS seems to reduce daytime sleepiness in most of the evaluated cases, even in subjects without reduced seizure frequency, and no correlation between modifications in sleep EEG composition and clinical response to VNS has been stated. Based on this currently available literature, we can conclude that, until today, it is not possible to predict (a future) clinical response to VNS by evaluating (subjective) sleep measures as daytime sleepiness and modifications in sleep EEG. However, further prospective, large sample size studies are recommended to confirm this statement.
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