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Effects of antiepileptic drugs on sleep architecture

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Effects of antiepileptic drugs on sleep architecture

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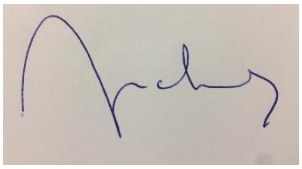
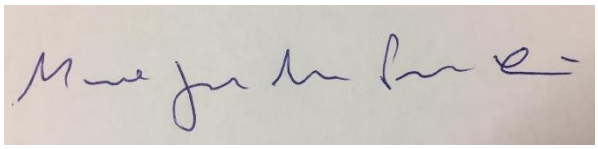
Assinatura do Estudante



Assinatura do Orientador



Assinatura do Coorientador

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Index of abbreviations

AASM: American academy of sleep medicine

AED: Antiepileptic drugs;

BZD: Benzodiazepine;

CBZ: Carbamazepine;

CLO: Clobazam

CLN: Clonazepam;

EDS: Excessive daytime sleepiness;

EEG: Electroencephalogram;

EMG: Electromyography;

EOG: Electro-oculography;

ETX: Ethosuximide;

FBM: Felbamate;

GBP: Gabapentin;

LCS: Lacosamide;

LEV: Levtiracetam;

LTG: Lamotrigine;

MSLT: Multiple sleep latency test;

MWT: Maintenance of wakefulness test

NREM: Non-rapid eye movement;

PB: Phenobarbitone;

PGB: Pregabalin;

PHT: Phenytoin;

PER: Perampanel

PSG: Polysomnography;

PWE: Patients with epilepsy;

REM: Rapid eye movement;

RLS: Restless leg syndrome;

SE: Sleep efficiency;

SWA: Slow-wave activity;

SWS: Slow-wave sleep;

TGB: Tiagabine;

TST: Total sleep time;

TPM: Topiramate;

VGB: Vigabatrin;

VPA: Valproic acid;

WASO: Wake after sleep onset;

ZNS: Zonisamide;

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Resumo:

Introdução: O sono fisiológico e reparador é fundamental para um bem-estar físico e mental sendo também necessário à manutenção da função imunológica e cognição. O sono pode ser estudado recorrendo a escalas que graduam a sua qualidade ou então recorrer a métodos objetivos, como a polissonografia, que quantifica os parâmetros da arquitetura do sono e é mais rigorosa do que métodos subjetivos. A interferência dos fármacos antiepiléticos, usados não só na epilepsia, não é ainda bem conhecida, principalmente no que concerne aos novos antiepiléticos.

Objetivos: Revisão sistemática da literatura relativa à influência na arquitetura do sono dos fármacos antiepiléticos para perceber se os novos fármacos têm melhor perfil na estrutura do sono do que os mais antigos.

Métodos: Foi feita uma pesquisa bibliográfica na Pubmed e Scopus usando as palavras-chave "sleep" e "antiepileptic drugs", bem como uma pesquisa individual para cada antiepilético combinado com "sleep". Excluímos terapêuticas cirúrgicas, artigos que estudem o sono em idade pediátrica ou com modelos animais.

Resultados: Foram incluídos 62 artigos, dos quais 21 eram randomizados, controlados e duplamente cegos. Foram incluídos artigos em doentes com epilepsia, mas também em doentes com síndrome das pernas inquietas, bruxismo, insónia primária, fibromialgia e apneia obstrutiva do sono, bem como em indivíduos saudáveis. Dos fármacos antiepiléticos clássicos a carbamazepina é o mais estudado, tendo um efeito negativo no sono enquanto o fenobarbital tem um efeito dose-dependente no sono. O ácido valpróico tem pouco ou nenhum efeito sobre os parâmetros do sono. Não foi possível estabelecer conclusões sobre a fenitoína. No grupo dos novos fármacos antiepiléticos, o clobazam, o clonazepam, a gabapentina, a lacosamida, a lamotrigina, o perampanel, a pregabalina e a tiagabina parecem ter um efeito positivo na estrutura do sono. O topiramato e a zonisamida não interferem no sono enquanto o levetiracetam pode ter um efeito negativo na sua estrutura.

Conclusão: O número de ensaios clínicos randomizados e duplamente cegos sobre a arquitetura do sono é bastante escasso pela dificuldade de acesso da polissonografia em laboratório. Também as metodologias que encontramos foram bastante heterogéneas, o que limitou o estabelecimento de conclusões e impossibilita fazer meta-análise. Os fármacos mais antigos parecem, de uma maneira geral, ter uma interferência negativa, enquanto os mais recentes parecem não alterar ou até ter ação benéfica na estrutura do sono. Serão necessários estudos futuros controlados para

estabelecer conclusões mais significativas sobre o impacto deste grupo de fármacos na arquitetura do sono.

Abstract

Introduction: Physiological and restorative sleep is fundamental for physical and mental well-being and is also necessary for the maintenance of immune and cognitive function. Sleep can be studied using scales that rank its quality or resort to objective methods, such as polysomnography, which quantifies the parameters of sleep architecture. The polysomnographic parameters, being objective, give us a view with less sleep bias compared to subjective methods. Antiepileptic drugs are a group of drugs used not only in epilepsy. Its interference in the sleep structure is still not well known, especially with regard to the new Antiepileptic drugs.

Objectives: Systematic review of the literature on the influence of Antiepileptic drugs on sleep architecture attempts to detect whether the new antiepileptic drugs have a better profile on sleep structure than the older ones.

Methods: A bibliographic search was performed in Pubmed and Scopus, using the keywords "sleep" and "antiepileptics", as well as a search for each drug combined with "sleep". Surgical therapies and articles in pediatric age or animal studies were excluded.

Results: 62 articles were included in our review, of which 21 were randomized, controlled and double-blinded. The articles were included in patients with epilepsy, but also in patients with restless leg syndrome, bruxism, common insomnia, fibromyalgia and obstructive sleep apnea, as well as in healthy individuals. Among classic antiepileptic drugs, carbamazepine is the best studied antiepileptic drug. It has a negative effect on sleep while phenobarbitone has a slightly dose-dependent interference effect on sleep. Valproic acid has little to no effect on sleep architecture. Any conclusion can be drawn about phenytoin. In the newer antiepileptic drugs group, clobazam, clonazepam, gabapentine, lacosamide, lamotrigine, perampanel, pregabaline and tiagabine seem to have an overall positive profile in sleep structure. Topiramate and zonisamide appear to be innocent while levetiracetam can have a negative profile in sleep.

Conclusion: The number of randomized, double-blind clinical trials on sleep architecture is quite low due to the difficulty of accessing polysomnography in the laboratory. Also, the methodologies found were quite heterogeneous, which limited the establishment of conclusions and made it impossible to carry out meta-analysis. Globally, newer antiepileptic drugs appear to have an innocent or positive effect on sleep structure when compared with older ones but future controlled studies will be needed to establish more significant conclusions about the impact of this group of drugs, widely used in various pathologies, on sleep architecture.

Keywords: Antiepileptic drugs; sleep; polysomnography.

Introduction / Objectives

A good night of sleep is recognized as essential to optimal physical and mental health. The impact of sleep in the immune system functioning and cognition has already been described [1]. The recommendation of the American Academy of Sleep Medicine (AASM) and the Sleep Research Society is, for adults up to 60 years of age, to sleep seven or more hours on a regular basis [2]. Sleeping impairment may lead to excessive daytime sleepiness (EDS), with drowsiness occurring in situations in which an individual is expected to be alert and vigilant [1]. Concomitantly, EDS can also be seen when the total sleep time (TST) is within normal range, particularly when there is sleep fragmentation, defined by recurrent arousals and/ or stage shifts[3]. Early detection of sleep disorders is important, mainly due to its impact on general public health, contributing to an overall increase in the population's morbidity, mortality and decreased work productivity. A correct diagnosis and management is usually possible and may improve health and quality of life of patient with sleep disorders [2, 4].

Sleep structure can be subjectively assessed by self-reported sleepiness quantification scales, such as the extensively used Epworth Sleepiness Scale or the Stanford Sleepiness Scale. These two subjective methods are considered to be more inaccurate in their correlation with sleep structure and, therefore, objective methods are preferred [1]. To the date, traditional in-lab polysomnography (PSG) is still the gold standard for objective assessment of sleep structure [4-6]. Despite of this, home actigraphy, performed for one to two weeks, is being increasingly preferred to PSG, because it is a cheaper and an easier exam. Together with the maintenance of wakefulness test (MWT), that is the most commonly performed objective method for determining the treatment effects on sleeping and daytime sleepiness [2]. Daytime sleepiness can also be objectively assessed, in an ambulatory setting, through the multiple sleep latency test (MSLT) and MWT [4-6].

According to the AASM scoring rules, to determine sleep structure by PSG, the use of electroencephalogram (EEG), electromyography (EMG) for muscle tone and electro-oculography (EOG) for eye movements is mandatory and the scoring is done in 30-second periods called epochs [1]. Through this standardized PSG exam, sleep can be divided into two main stages: rapid-eye movement (REM) stage and non-rapid eye movement (NREM) stage. In its turn, NREM can be further divided into stages N1, N2 and N3. Before 2007, there was a NREM N4 stage which no longer exists and is now encompassed as part of N3 stage, sometimes called slow wave sleep (SWS) [1, 7]. Most individuals begin to sleep in a short NREM N1 stage, followed by the N2 stage and, finally, the REM stage, in a repetitive pattern of four to five cycles in every eight hours night sleep [7, 8]. To allow

the comparison of results, it is recommended that the stages are presented as a percentage of TST, since the total sleep time can widely vary among individuals [9].

Stage N1 is the lightest stage of sleep and its increase suggests sleep fragmentation. Stage N2 usually comprises the highest percentage of TST in adults, when lasting longer is most commonly associated with benzodiazepine (BZD) use. In young adults, SWS comprises about 20% of TST and decreases with age [1, 7]. Declarative memory consolidation is essentially supported by this stage, mainly by slow oscillations <1 Hz. Although SWS is considered the deepest and most restful stage of sleep, its contribution to the subjective perception of a "good night sleep" is still uncertain [1, 7, 10, 11]. The REM stage, in which dreams occur, seems essential for the non-declarative, procedural and emotional memory consolidation [12]. Characteristic of each PSG stage is described in table I.

In addition to the sleep stages, there are other sleep parameters that can also be assessed. Arousals occur when, during the deep sleep stage, one experiences a lighter sleep stage or wakefulness. Specific EEG criteria in NREM and REM sleep must be detected in order to classify this shift as an arousal [1]. Sleep efficiency (SE), expressed as a percentage, is calculated by dividing the TST by the time spent in bed. Latency to a sleep stage, expressed in minutes, is the time spent from sleep onset to the first epoch of that stage. Awakenings are only considered when EEG returns to the waking background rhythm for at least 30 seconds. Wake after sleep onset (WASO), expressed in minutes, is defined as the periods of wakefulness that occur after defined sleep onset and excluding those before sleep onset. It is considered an important indicator of sleep fragmentation [3].

Although most changes in sleep structure are considered deleterious, there are some which are seen as improvements, such as a decreased number of arousals and/ or N1 stage and an increased SWS or REM stage [6].

Antiepileptic drugs (AEDs) are a heterogeneous class of drugs used worldwide, mainly to prevent epileptic seizures. These can be classified according to their mechanism of action or, alternatively, in classic AEDs or new AEDs, as shown in Table II. In theory, the new AEDs have fewer side effects. AEDs are not used exclusively in epilepsy, in fact, its use has been expanded to treat other pathologies, such as neuropathic pain [13], fibromyalgia [14], mood disorders [15], bruxism [16], restless leg syndrome (RLS) [15] or periodic limb movement disorder [17]. The current knowledge is that all AEDs can influence sleep architecture, but there may be a positive or negative impact caused by the drug *per se* or by the type of epilepsy [18]. Sleep disturbances can also exacerbate the drowsiness and memory dysfunction, common in patients with epilepsy (PWE), and be a factor itself of difficulty in controlling seizures [19]. According to the reported literature, it is known that most of the classic

AEDs have a detrimental effect on sleep. On the other hand, although the literature is scarce in relation to objective analysis of sleep, the newer AEDs do not seem to affect nocturnal sleep as much and some may even improve sleep parameters [20]. This sleep stabilization may be directly related to the intake of AEDs or, rather, a consequence of seizure control [21]. Polytherapy is also an independent risk factor for EDS, with patients taking more than one AED being at higher risk than those on monotherapy [22, 23].

It is known that sleep disturbances are associated with decreased quality of life in chronic diseases such as epilepsy [5]. In PWE, a group with a particularly high incidence of sleep-related complaints, sleep disorders represent an increased risk in seizures control [4, 6]. PWE have a higher frequency of arousals, awakenings and phase shifts compared to the general population, even when they are controlled or without AEDs treatment [24]. These three abnormalities increase ictal and interictal epileptic phenomena, which can also alter the sleep-waking cycle and sleep architecture [6, 25].

Despite their extensive use, objective influence of AEDs on sleep has not yet been broadly studied [21]. Since drowsiness is one of the most common reported side effects, some direct influence may indeed be suggested [6]. Maestri et al in de novo untreated PWE have already concluded that there were no significant differences regarding sleep parameters compared to the control group and, thus, EDS may be due to a factor other than epilepsy *per se* [26]. Larger studies are needed to confirm this conclusion, but this is a challenging task, as testing the long-term effect of most AEDs in individuals without epilepsy is unethical, preventing the formation of larger control groups, and it is dangerous to switch of the AEDs in PWE just to control these confounding factors [27]. There is not enough research with focus on non-BZD to conclude its usefulness and safety in insomnia's treatment, because designing large trials without bias are complicated and expensive [28].

The aim of this review is to study the direct influence of the newer AEDs on sleep architecture, as well as to compare such parameters with the classic AEDs. With this, we intend to better understand the effect of AEDs not only in the treatment of epilepsy but also in other pathologies in which AEDs are used.

Methods

Our research was carried out, from September 1st to October 1st 2019, in PubMed and Scopus databases, using the MESH-terms "Antiepileptic drugs" AND "sleep" as keywords.

Only clinical trials with individuals treated with acute or chronic AEDs and written in English were selected.

In this review, we included trials in which the effects of AEDs in participants without epilepsy, but with other pathologies and in healthy adults was studied. Trials involving children or concerning non-pharmacological treatments of epilepsy, such as vagus nerve stimulation or surgery, were excluded. We chose not to impose any temporal limits, since part of the available literature on this subject was published more than twenty years ago. The search conducted in the aforementioned databases also combined individual AED names with "sleep" (for example "carbamazepine AND sleep"). After removing all duplicated articles, the results were added to the first search, as shown in table III. The classic AED searched were carbamazepine, phenobarbitone, phenytoine and valproic acid. The newer AED searched included clobazam, clonazepam, eslicarbazepine acetate, ethosuximide, felbamate, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, pregabalin, stiripentol, tiagabine, topiramate, vigabatrin and zonisamide. Multiple articles concerning BZDs were obtained, however, in our review, we only focused on clonazepam and clobazam, because these are also used as AEDs. Other trials including BZD were excluded.

The articles selected for qualitative review included only the ones that assessed objective sleep outcomes. Articles concerning only subjective sleep outcomes were excluded. The objective sleep outcomes considered were the PSG measurements previously described, such as sleep stages and other sleep parameters. Articles reporting MLST results were also included, as this is a validated objective parameter. In this review, studies considering the old classification of stages N3 and N4 were reported here as slow wave sleep (SWS). The class of evidence was based on the recommendations from American Academy of Neurology [29].

Results

After the bibliographic search, summarized in table III, sixty-two articles were selected to qualitative analysis. Twelve focused only on classic AEDs, forty-three focused exclusively on one of the newer AEDs and seven assessed more than one AED simultaneously. Tables IV, V and VI summarize the significant results reported in the articles selected for analysis.

We found twenty-one randomized, double-blind studies, placebo-controlled (Class I evidence), nine class II studies, thirty class III and two class IV considering the effects of AEDs with objective measure of sleep architecture parameters.

Classic AEDs

1. Carbamazepine

Seven papers were obtained concerning carbamazepine (CBZ), with the best evidence being a class II trial in psychiatric disorders [30] and the rest were all class III of evidence. This AED was primarily associated with a significative increase in SWS and a concomitant decrease in the REM stage in healthy volunteers in a class III article [31]. Subsequent trials confirmed this by using CBZ in acute treatment of patients with focal epilepsy [32, 33], psychiatric disorders [30] and in healthy volunteers [34]. In a smaller study, conducted in healthy individuals, CBZ also appeared to improve sleep continuity and efficiency [35]. Another longitudinal trial reported an increase in SWS after using CBZ in PWE, but without significant differences concerning the REM stage [36]. Gann et al described a higher SE and a decrease in N2 stage[34].

The impact of chronic CBZ treatment in sleep parameters was assessed by Manni et al on an observational, small sample, non-controlled study. These authors found an overall decrease in the latency and percentage of REM stage, a reduction in sleep stability, with a greater number of stage shifts, and a reduction in the number of awakenings. However, it is necessary to consider the small sample of this study, with only eight focal epilepsy patients with complete seizure control and six subjects with poor seizure control [32]. In the opposite, Legros et al. reported a non-significant decrease in REM sleep and supported the idea that chronically administered CBZ does not significantly affect sleep [37].

In the most recent articles, some sleep parameters, such as higher cyclic altering pattern rates during NREM and arousals, appear to be worse than in drug-naïve individuals. Therefore the authors concluded that CBZ negatively affects sleep quality in this patients subgroup. Since drug exposure was not controlled, it is not possible to conclude whether sleep changes are caused by the underlying disease or by exposure to CBZ [38].

Although CBZ initially has a deleterious effect on sleep, namely through the reduction of REM sleep, in the long-term, it does not seem to significantly modify this parameter. The authors suggest that those effects may only be acute and temporary [33, 37, 39].

Despite of CBZ being extensively used in neuropathic pain such as trigeminal neuralgia, we have not found papers concerning this patients group.

The low level of evidence, due to the lack of class I studies, prevents definitive conclusions about the impact of CBZ on sleep structure. However, in acute therapy, most articles seem to point

to an increase in SWS and a decrease in the REM stage. In chronic intake, there is less evidence of sleep disturbances.

2. Phenobarbitone

Phenobarbitone (PB) is a sedative agent, sometimes used as a hypnotic. For this reason, evident changes in sleep architecture were expected [40]. Four articles on PB were found, of which only one was class I and the others were only class III of evidence.

The best evidence comes from a study performed by Karacan et al in healthy individuals that found a dose-dependent reduction in REM sleep, the main change of PB in sleep architecture. The authors also reported a reduction in stage shifts and number of awakenings and an increase in SL and N2 stage [41]. Also in healthy individuals, Prinz et al found no differences in immediate acute monotherapy compared to placebo. However, after one month undertaking PB, a significant reduction in SL and SWS was observed [42].

On PWE, Wolf et al found remarkable acute changes in PSG compared to baseline. In generalized epilepsy, PB diminished REM interruptions and showed a tendency to decrease SWS [43]. On MSLT, Manni et al reported a greater propensity to daytime sleep in generalized epilepsy treated with PB compared to focal epilepsy treated with CBZ or healthy controls. However, no changes in sleep architecture were found in PSG sleep variables [44].

3. Phenytoin

This review included four articles concerning phenytoin (PHT) use in PWE. Unfortunately, all of them were class III evidence.

Roder-Wanner et al. conducted the only trial in which PHT is studied alone. They conclude that PHT increased SWS, while reducing NREM sleep, and managed to differentiate a modest acute change in sleep, from a more prominent 6-weeks effect [45] These authors also stated that, with continuous administration, the third REM-cycle was consistently the most affected and found a diminished sleep latency.

In a crossover study with phenobarbitone, Wolf et al also reported an increase in SWS and decreased sleep latency, but without a significant reduction in REM stage [43].

In an observational study, Drake et al included five patients chronically treated with PHT and noticed a decreased in TST. Like Wolf et al, these authors found little to no effect on REM sleep, but, conversely, they noticed an increase in sleep latency [46]. Despite the discordant results, we need to consider that this study was conducted in a very small sample and with uncontrolled PHT dose-exposure.

Legros et al, in an observational and uncontrolled trial, found an increase in N1 stage, while observed a modest decrease in the REM stage, in agreement with previous studies. However, they reported a decrease in SWS, conflicting to previous studies. The small sample of this trial, including only seven PWE, limits the conclusions' validation. Additionaly, it also has the disadvantage of including patients with an acute withdrawal of AEDs, whose effects on sleep cannot be excluded [37].

4. Valproic acid

Five articles regarding valproic acid (VPA) were eligible for this review but only one was class II and the rest class III of evidence.

The best evidence comes from a double-blind, placebo controlled cross-over with levodopa trial in patients with RLS in which VPA appears to have an innocent impact in sleep parameters, except for increased N2 latency compared to placebo [47]. In most studies, VPA has been associated with attention impairment during the day by increasing N1 sleep and decreasing SWS [46, 48], however minimal to no effects on sleep architecture were demonstrated [46, 47, 49].

In healthy adults, 500 mg/day of VPA appears to reduce REM stage and increase SWS, this changes are more pronounced with 1000 mg/day compared to placebo [49].

In PWE, both Wolf et al and Legros et al reported an increased N1 stage as the only change in the sleep parameters of the VPA subgroup [37, 50]. Drake et al reported a slight increase in SWS, but their observational study only included five patients on VPA monotherapy and they used an ambulatory EEG record instead of an in-lab PSG [46].

Newer AEDs

1. Clobazam

Most clinical trials on the influence of clobazam (CLB) on sleep are studied in children and, therefore, these articles could not be included in this review.

The evidence available in adults is from only one class I, randomized, double-blind study in healthy volunteers performed by Nicholson et al. The authors used doses of 10mg and 20mg of CLB. The lower dose decreased the percentage of stage N1 and SL compared to placebo. By doubling the dose to 20mg, the effects on stage N1 and SL were more pronounced, with the authors also describing a decrease in stage N3 and SWS and noting an increase in stage N2. [51] Conclusions based in only one paper are not possible to be made.

2. Clonazepam

Although clonazepam (CLN) is extensively used in sleep disorders, the available literature on its impact on sleep structure is scarce [52]. Only five articles were found, four of wich class III and only Sakai et al present a class I study [53]. They reported non-significant changes in patients with sleep bruxism undergoing CNZ compared to placebo. This remains the highest quality evidence on CLN although we can consider that the crossover with clonidine can be a confounding factor for the results presented [53].

Drake et al were the first authors to study CLN's influence on sleep. This trial was conducted in healthy adults and they found a reduction in SL and REM latency [46]. Saletu et al described a relatively positive sleep profile with 1mg of CLN compared to placebo in patients with sleep bruxism [54]. These patients suffered from fewer awakenings, longer TST, reduced WASO, greater SE, less stage shifts and an increase in stage N3, while stage N1 decreased [54].

In an observational study conducted in patients with idiopathic REM Sleep Disorder, the authors described the lack of objective effects of CNZ in REM sleep parameters, but evidence of NREM sleep disturbance was found in a group of these patients on chronic use of CNZ. The retrospective design, the heterogeneity of sample size and disease`s duration of the study decreases its level of evidence. Nonetheless, after 2,5 years of follow-up, they concluded that CLN decreases NREM sleep instability, increases N2 stage and decreases WASO relative to baseline [52]. The author confirmed these findings with a new longitudinal study, but no significant results were found in patients undergoing acute monotherapy [55].

3. Ethosuximide

The only article found on ethosuximide was an observational class III study conducted in PWE, with absence seizures, by Wolf et al. They found a significant increase in N1 sleep and a concomitant reduction in SWS [50]. As prospective and randomized trials are lacking, these findings have low level of evidence.

4. Felbamate

The only published study on felbamate (FBM) was a case report that suggested a reduction in phase-shifts, nocturnal awakenings, N1 stage and WASO and an increase in the sleep efficiency index [56]. This class IV evidence is insufficient to draw conclusions about FBM effects on sleep.

It is known that FBM has a stimulating profile, being responsible for insomnia, anorexia and anxiety in focal epilepsy, lacking anxiolytic effects. Thus, a formal evaluation of sleep parameters should be performed (56).

5. Gabapentin

Gabapentin (GBP) is one of the best studied AEDs, with nine articles included in our review, two of them class I, three class II, three class III and one class IV of evidence. It is curious that, although GBP is widely used in neuropathic pain, no study has been designed in these pathology. The most common findings, reported in almost every study about GBP, is an increase in SWS and in the N1 stage, with variable effects in REM sleep.

The most objective and robust evidence on GBP was provided by a large multicenter, randomized class I clinical trial. The authors studied the GBP effect on sleep compared to placebo, in adults without epilepsy, but with sleep complaints. A dose of 250 mg and 500 mg of GBP was administered thirty minutes before bedtime and the results demonstrated an increase in TST and in sleep depth in both gabapentin users. Therefore, GBP has beneficial effects on sleep, contributing to a longer sleep duration and greater depth of sleep [57]. Another class I paper also in healthy adults, confirmed an increase in TST and a decrease in WASO, in line with the previous studies. Authors also found a small but significant decrease in the REM percentage and slight increase in the N1 stage [58].

The oldest GBP study was a class II trial conducted in six healthy adults, so it is not possible to extrapolate the results. The authors found that GBP had no effect on TST, REM or REM latency,

but increased SWS and decreased sleep latency [59]. In another class II sleep bruxism patients trial, GBP contributed to a significant reduction of bruxism episodes per night, suggesting that it could be an effective alternative treatment. This AED significantly increased the TST, SE and N3 stage compared to a stabilization splint [16].

Although GBP worsens apnea and respiratory indexes in healthy non-obese adults, the most recent class II trial on sleep apnea found no significant effects on sleep architecture [60].

Legros et al. conducted a class III observational study that, among other AED, contained a subgroup with only three PWE using GBP and they found no significant differences between these drug-users versus placebo. Due to its small sample, it is not possible to generalize these results [37].

An open-label class IV study with GBP reported an increase in SE and SWS and a decrease in the arousal index, without affecting any other sleep parameters. The methodological flaws of this study were highlighted in a letter to the editor, published in the same journal, questioning its real relevance to the current evidence [61, 62].

6. Lacosamide

Two studies concerning lacosamide (LCS) and sleep architecture were obtained.

Foldvary-Schaefer et al. perform the first class I trial in PWE that provide the most robust evidence, that indicated that LCS is not a major contributor to EDS, although there is an elevated prevalence of EDS in these patients. At baseline and at follow-up, the only significant change compared to placebo was a reduction in the arousal index, suggesting a positive effect of LAC use. However, the study's short duration and the recruitment from a single site limit the generalization of these findings [24]. This innocent role of LCS in sleep supported the previously published class III study by Hudson et al. research in healthy individuals [63].

7. Lamotrigine

Three articles focused on use of lamotrigine (LTG) in focal epilepsy patients were obtained. All of them are class III evidence.

Clinically, LTG is not associated with EDS and most studies indicate an improvement in sleep stability [20, 64]. Legros et al. found no statistically significant differences in sleep architecture in the four patients using LTG [37]. The other two studies, both open label, commonly found a reduction in

SWS. Placidi et al. found a significant increase in REM sleep, a reduction in the number of REM entries and phase shifts and a lack of negative effects on daytime somnolence in drug-resistant PWE using LTG as a chronic add-on medication [20]. On the other hand, Foldvary et al found an increase in the N2 stage and less stage shifts and arousals, suggesting LTG as a less sleep-disturbing drug than older AEDs [64].

There is still no evidence regarding the effects of LTG on healthy individuals to allow conclusions, but in PWE it is associated with positive effects on sleep. We have also found no studies on mood disorders, even though LTG is widely used in these psychiatric disorders.

8. Levetiracetam

Levetiracetam (LEV) has been recently associated to a higher total sleep duration, even though sleep complaints are not a commonly reported adverse effect of this drug [65]. We found six reports evaluating sleep parameters in subjects taking LEV with very heterogeneous results. Two were class I evidence, two class II and two class III.

Bell et al. designed two studies. The first was a class I conducted in healthy individuals and the second one was a class II in focal epilepsy patients taking concomitantly CBZ. They concluded that LEV increased the N2 stage, in both groups. In healthy adults, LEV increased REM latency and decreased N4 sleep in patients with focal epilepsy. Unlike BZD, it does not seem to affect sleep continuity, although a subjective reduction in sleep perception was observed [66] The best evidence on LEV that we found came from a study performed by Cicolin et al (65). It is a randomized, double-blind design with higher dose of LEV 2000 mg/day, in healthy volunteers, that found and reinforce the increase in the N2 stage. In MSLT the sleep latencies were normal and they also did not find any abnormalities in MSLT and thus the authors considered that LEV at therapeutic dose for epilepsy stabilizes sleep without affecting daily activities.

In a small class II study performed by Bazil et al, LEV seemed to have only minor implications in sleep structure, with the only relevant difference being an increase in the number of awakenings [19]. Also with a dose of 1000mg/day, Zhou et al only observed a reduction in REM sleep time after LEV treatment, on PSG evaluation. They reported no changes in MSLT.

Using actigraphy and MWT on focal epilepsy subjects, Yilmaz et al observed that, after three weeks of LEV, there was an increase in daytime napping episodes and total nap duration while there was a decrease in total activity score at night as in monotherapy or as in an add-on with another

AED. The authors point out that although actigraphy gives a good measure of sleep continuity, it is not as efficient in assessing sleep architecture and these results must be confirmed by PSG [67].

In a crossover trial with CBZ in newly diagnosed focal epilepsy patients, Cho et al described that LEV increased sleep efficiency, reduced WASO and did not have overall major effects in sleep structure as opposed to those on CBZ [36].

9. Perampanel

We obtained only two articles regarding the effects of perampanel (PER) on sleep parameters [18, 68]. Both were class III evidence but one of them in PWE and the other in patients with restless legs syndrome (RLS).

PER is known to cause EDS. This is the most commonly reported adverse effect in these trials and, therefore, it is recommended to be taken before bedtime. [18] A positive sleep profile was subjectively described when PER was used as an adjunctive drug. In an exploratory study done by González-Cuevas et al, in patients with focal epilepsy in adjunctive treatment with PER, the drug was well tolerated and did not cause any somnolence or modification in sleep parameters [68]. Garcia-Borreguero et al comment on these findings in their open-trial in RLS patients. Unlike previous authors, they described many modifications on objective sleep outcomes. In monotherapy, PER increase TST, SE and arousals, and decreased SL and WASO. Regarding the sleep stages, the SWS increased and the N1 stage decreased. It did not affect the duration or percentage of REM, but it did reduce its latency [18].

Both studies were class III with uncontrolled design and a small sample, ten and twenty individuals, respectively. There are still no large randomized, controlled clinical trials on PER to establish definitive conclusions.

10. Pregabalin

Seven articles were obtained on the effect of pregabalin (PGB) on sleep parameters. Three of which were class I evidence and three class II and one class III. PGB is also used in fibromyalgia and neuropathic pain but none article comprising these subgroups of patients was selected for review.

The only randomized clinical trial conducted in healthy adults described an increase in TST and in SE and a decrease in SL and in the number of awakenings, shorter or longer than one minute.

Regarding sleep stages, the SWS increased and the duration of REM sleep was reduced. No disturbances were found in REM latency [10]. Another randomized study, conducted in patients with RLS, had the most controlled design and also the largest sample, with a total of seventy-five PGB users. The authors found a reduction in WASO and the number of awakenings, making it better than placebo in improving sleep disturbances, as assessed by objective and subjective sleep parameters [69].

Garcia-Borreguero et al found an increase in SE, an increase in the percentages of stages N1, N2 and N3 and in minutes of SWS and WASO, after three weeks of PGB in patients with idiopathic RLS. There were no changes in REM, in TST, SE or sleep latencies [69].

In patients with focal epilepsy, after four weeks of adjuvant therapy with PGB in individuals with sleep complaints, an improvement in sleep continuity was demonstrated in a class II study. This was due to a reduction in WASO and in the number of awakenings and an increase in SE. The authors complain about the small sample used, mentioning difficulties in recruiting patients [5]. In a similar group of patients, Bazil et al did not find any of these changes but in turn found a significative increase in SWS percentage and a modest reduction in stage N1 sleep [70]. In a group of twelve patients with focal epilepsy without sleep complaints, after three months adjuvant therapy with PGB, Romigi et al reported only a significant increase in REM sleep and a reduction in the N2 stage compared to baseline [23].

11. Tiagabine

Tiagabine (TGB) is the best studied AED regarding objective sleep parameters, with nine articles obtained, seven of them are class I. The other two were class II and class III evidence.

Mathias et al were the first to describe a higher number and frequency of arousals in placebo group, rather than in the TGB group, in healthy subjects at a 5mg dose. The authors showed that patients from TGB group have greater sleep efficiency and SWS [71].

During a sleep restriction period of four nights and with 8mg of TGB, Walsh et al were the first authors to describe an improvement in the SWS compared to baseline and placebo [72]. In an exploratory study with healthy elderly individuals, Walsh et al found a positive effect on sleep with a 4mg or 8mg dose of TGB. No differences were found between placebo and 2mg of TGB. Those results demonstrated an improved sleep maintenance by decreasing WASO and/or stage N1 as well

as increasing SWS [73]. On this study, patients had no subjective complaints concerning sleep and the reduction found in stage N1 may result from increasing time passed on SWS which reduces arousability [73]. Only studies with a larger sample will provide a clear assessment of the various doses of TGB in the PSG variables [73].

In older adults with primary insomnia, TGB shows a dose-dependent increase in SWS [74, 75], at doses up to 8mg. It does not appear to increase sleepiness in the following morning, but it did show a reduction in the duration of stage N1 [75].

In a study by Walsh et al. TGB seems to decrease the biological consequences of sleep restriction [72]. However, in a subsequent trial, memory consolidation did not improve [11].

A double-blind crossover study by Feld et. al showed that TGB improves SWS and decreases REM without affecting subjective sleep perception or improving memory consolidation. They proposed that TGB-induced SWS is functionally different from normal SWS. This may be the possible reason why it fails to improve memory consolidation. [11] WASO, LPS, and TST, which are the traditional variables of hypnotic efficacy, were not modified by TGB in any dose in a study performed by Walsh et al (2006) [28]. Only the group of patients with a TGB dose of 10 mg, the maximum dose in the study, reported morning sedation [28]. In the largest sample study TGB significantly increased SWS at any dose, while decreasing N1 stage [28]. Compared to placebo, TGB showed an increased in slow-wave activity on EEG, but no SWS duration abnormalities during sleep were observed [76]. It has also failed to increase N3 sleep in patients with obstructive sleep apnea [76].

12. Topiramate

Only one class III article was selected. Bonnani et al reported the absence of significant changes in objective sleep parameters in PSG or MSLT in PWE taking topiramate (TPM) [77]. Interestingly in this study is that it goes against the common subjective description of drowsiness related to TPM. Although prospective, the quality of the evidence provided by this study is low, due to its lack of randomization or concealment. Additional studies are needed, as topiramate (TPM) is an extensively used medication, not only in epilepsy but also on other pathologies, such as headaches, essential tremor and weight control [77].

13. Vigabatrin

Bonnani et al reported no changes in sleep structure when vigabatrin (VGB) was used as an add-on to CBZ. However, some cases described a higher subjective level of somnolence compared to CBZ monotherapy [39]. This class III study was not a randomized trial, nor had a blinded intervention, but it remains the only objective sleep study on VGB.

14. Zonisamide

Two articles, one class II and another class III were collected.

In a class II randomized, placebo-controlled but with an open extension phase study on patients with sleep apnea, Eskandari et al reported no changes in sleep parameters within four weeks of treatment. Sleep apnea events were less frequent with ZNS, regardless of the reduction in body weight, probably due to the inhibition of carbonic anhydrase mechanism [78]. This, theoretically, could result in an improvement of EDS, but this benefit was not seen in the study.

In their observational study, Legros et al included one patient with zonisamide (ZNS) treated focal epilepsy. They found no significant changes in sleep parameters compared to healthy controls. A prospective study made by Romigi et al in focal epilepsy reported only a slightly greater number of awakenings [79]. However, the authors warned of the small sample and the open design study, which did not allow the generalization of the results.

15. Brivaracetam, Oxcarbazepine, Eslicarbazepine acetate and Stiripentol

We found no articles concerning brivaracetam, eslicarbazepine acetate, oxcarbazepine or stiripentol effects on objective sleep parameters. Recently Assenza et al in their multicenter study pointed out that ESL led to lower subjective feelings of drowsiness, so its objective study is of great interest [80].

Discussion

Most of the studies found were non-controlled studies or retrospective series of cases that have class IV of evidence, so in most of the AEDs any conclusion can be suggested, and in many others only a weak evidence-based recommendation can be established.

One of the objectives of this review was to compare classic and newer AEDs in terms of objective sleep parameters. After reviewing the literature and based on the reported results, we can recognize that newer AEDs are associated with less modifications in sleep architecture.

Among the classic AEDs, CBZ is the best studied AED. Its negative effects on sleep go through a reduction in REM phase and an increase in SWS. On other hand, PB seems to have an innocent or slightly dose-dependent interference effect on sleep. In most of the studies analyzed, VPA seems to have little to no effect on sleep architecture. PHT studies have low evidence level and conflicting data regarding its effect on sleep. Therefore, in absence of better data, we will not draw conclusions.

In the newer AEDs group, there are some AEDs, such as CNZ, GBP, LCS and PGB, which seem to have an overall positive profile in sleep structure. In PWE, LTG also appear to have a positive profile, but there is a lack of sufficient evidence to allow the generalization of the results in healthy population. TPM appears to be innocent to sleep architecture and it would be interesting to have new randomized studies, with larger samples to confirm this assumption. Others, such as LEV, despite improving SE and TST and not being associated with clinically evident EDS, caused changes on sleep architecture. These changes were not considered positive, once it increased stage N2 or reduced REM. CLB is rather ambiguous, in one randomized paper with a small sample, it is suggested a tendency to a deleterious profile, by reducing SWS and increasing N2. There are AEDs in which we cannot draw any conclusions like ETH, PNP and FBM, because there are no randomized studies yet. On FBM we only have a case report.

A limitation of our review was that we only selected objective studies in the qualitative analysis. Although less precise, subjective studies with validated questionnaires could be added in in further reviews. Another limitation was that the articles collected had very heterogeneous methodologies, either in terms of the objective method used (PSG, MLTS, or actigraphy) either in terms of dose of AED studied. Another point is that studies sometimes used old parameters like stage N4 because they predate the new classification. It was difficult to interpret results from very small samples and extrapolating conclusions in this context. In lab PSG is being less used for the diagnosis and characterization of sleep, being most of the time replaced by a more practical and easier assessment in an outpatient setting. Most data we found are from older articles and in recent years large studies using PSG are scarce. The heterogeneity of methodologies also precludes a meta-analysis of the results at this point.

Conclusion

The majority of the papers were class II or III of evidence and the number of randomized, double-blind clinical trials on sleep architecture is quite low due to the difficulty of accessing PSG in the laboratory. The exclusion of children limited even more our conclusions, but this was necessary as they have a very different sleep structure and lifestyle in comparison to adult population. The range of publication dates is also very wide due to the fact that AEDs are studied as to their effect on sleep closer to their release in the market. Thus the methodologies we found were quite heterogeneous, which limited the establishment of conclusions and made it impossible to do meta-analysis.

However, the older AEDs appear to have a more deleterious effect on the structure of sleep, while the newer ones appear not to alter and may even have a beneficial effect on the structure of sleep. Future controlled studies will be needed to establish more significant conclusions about the impact of this group of drugs, widely used in various pathologies, on sleep architecture. Researches regarding AEDs without class I articles, such as peranpanel, etosuximide and felbamate, or without any evidence at all, such as brivaracetam, eslicarbazepine acetate, oxcarbazepine or stiripentol, are even more needed.

Appendix

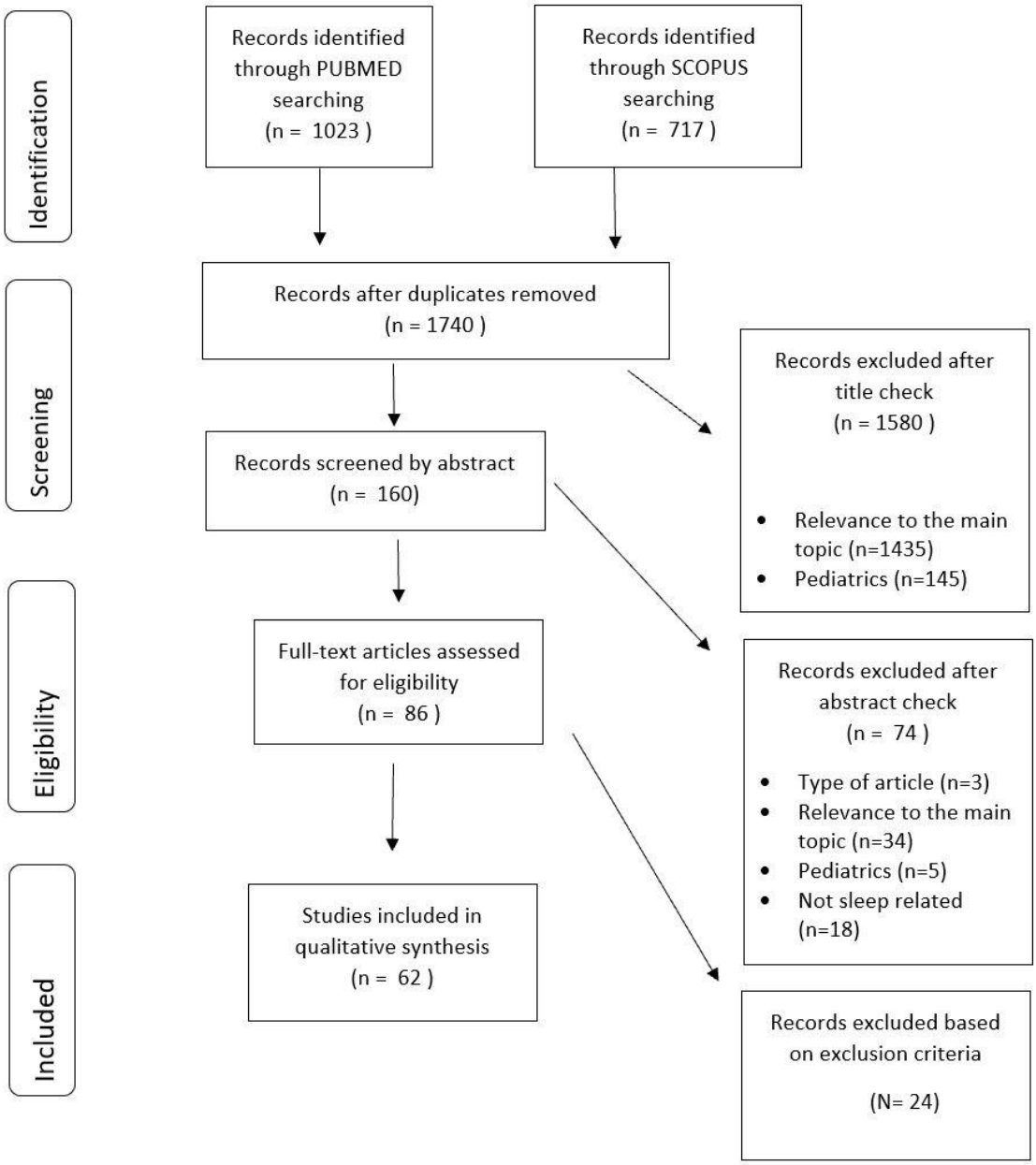

Figure 1. Paper screening methodology. Adapted from PRISMA. From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097.

Table I Summary of PSG characterization of sleep stages. EEG: Eletroencefalogram; EOG: Eletrooculogram; EMG: Electromyogram

	EEG	EOG	EMG
Stage N1	Low amplitude theta frequency	Slow-rolling ocular movements	-
Stage N2	Sleep spindles and k-complexes	Rolling ocular movements	Highest muscle tone
SWS	≥20% of the epoch with delta activity ≥75 mV of amplitude	-	Slightly reduced submental muscle tone
REM	Low voltage mixed pattern with "sawtooth waves"	Rapid, irregular eye movements, with initial phase less than 500 milliseconds	Atonia of all skeletal muscles

Table II Classification of antiepileptic drugs. AED: antiepileptic drugs

Classic AED	New AED
Carbamazepine	Briveracetam
Phenobarbital	Clobazam
Phenytoin	Clonazepam
Valproic Acid	Eslicarbazepine acetate
	Ethosuximide
	Felbamate
	Gabapentin
	Lacosamide
	Lamotrigine
	Levetiracetam
	Oxcarbazepine
	Perampanel
	Pregabalin
	Stiripentol
	Tiagabine
	Topiramate
	Vigabatrin
	Zonisamide

*Table III Summary of papers on classic antiepileptic drugs. (n=12). CBZ: carbamazepine; PB: Phenobarbitone; VPA: Valproic acid. *: p<0,05; **: p>0,01; ***: p<0,001.*

	Study	Type of study (class of evidence)	N	Population	Type of therapy	Dose (per day)	Comparison	Significative PSG Results (mean ± SD)
Carbamazepine	**Yang et al (1989)**	Prospective, non-randomized, non-blind. (Class III)	7	Healthy male volunteers	Acute monotherapy	Mean plasma range 11.8±1.1 µg/ml 200 → 700mg/day	NA	**↑SWS (%):** in CBZ (35.3±10.8) vs. Baseline (16.8±9.7)** **↓REM(%):** in CBZ (19.5±4.3) vs. Baseline (22.8±4.3)**
	Manni et al (1990)	Observational, non-randomized, non-blind. (Class III)	14	Focal epilepsy	Chronic monotherapy	15-20 mg/kg	Healthy controls (n=11)	**Patients with poor seizure control (mean 2.7 seizures per month; n=6):** **↓REM(%):** in CBZ (16.8±5.6) vs. Controls (29.6±5)* **↑REM latency (min):** in CBZ (140.4±32.5) vs. Controls (75.1±16.2)* **↑WASO:** in CBZ (42.5±17.4) vs. Controls (13.4±10.8)* **↑No. of awakenings:** in CBZ (10.3±4.0) vs. Controls (2.6±1.7)* **↑No. of shifts to stage N1:** in CBZ (13.0±6.8) vs. Controls (3.7±1.6)* **↑No. of stage shifts:** in CBZ (47.8±9.8) vs. Controls (21.0±4.5)* **Patients with complete seizure control (n=8):** **↑REM latency (min):** in CBZ (106.4±24.3) vs. Controls (75.1±16.2)* **↑No. of awakenings:** in CBZ (9.5±5.6) vs. Controls (2.6±1.7)* **↑No. of shifts to stage N1:** in CBZ (10.0±4.1) vs. Controls (3.7±1.6)* **↑No. of stage shifts:** in CBZ (40.0±10.5) vs. Controls (21.0±4.5)* **There were no significative differences between the groups.**
	Riemman et al (1993)	Prospective, non-randomized, non-blind. (Class III)	12	Healthy male volunteers	Acute monotherapy	400 mg/day	NA	**After 5-day course of CBZ:** **↑SE (%):** in CBZ (95.2±1.6) vs. Baseline (91.1±4.0)*** **↓N2 latency (min):** in CBZ (9.9±6.3) vs. Baseline (23.8±13.7)** **↓Wake time (%):**in CBZ (1.6±1.4) vs. Baseline (3.5±2.9)* **↑SWS (%):** in CBZ (13.2±7.0) vs. Baseline (6.8±5.3)** **↓Total REM density (%):** in CBZ (16.6±5.6) vs. Baseline (21.8±5.1)*
	Gigli et al (1997)	Prospective non-randomized, single-blinded (Class III)	16 (n=7 patients)	Temporal lobe epilepsy	Acute or chronic monotherapy	Initial dose: 400mg Following: 800mg	Healthy subjects	Acute CBZ in controls: **↑Stage shifts:** in acute CBZ (211.9±78.7) vs. Baseline (176.9±56.4)*** Acute CBZ in TLE: **↓REM(%):** in acute CBZ (14.1±3.9) vs. Baseline (17.6±4.8)** **↑No. of entries in REM:** in acute CBZ (44.9±12.3) vs. Baseline (31.6±5.8)** No significative changes in chronic CBZ

	Gann et al (1994)	Prospective, non-randomized, uncontrolled (Class III)	12	Healthy volunteers	Acute monotherapy	400mg/day	NA	**At night 5:** **↑SE(%):** in CBZ (95.2±1.6) vs. Baseline (91.1±4.0)***; **↓Stage N2 latency (min):** in CBZ (9.9±6.3) vs. Baseline (23.8±13.7)**; **↑SWS(%):** in CBZ (13.2±7.0) vs. Baseline (6.8±5.3)**; **↓Total REM-density (%):** in CBZ (16.6±5.6) vs. Baseline (21.8±5.1)*;
	De la Fuente et al (2002)	Randomized, single blinded (Class II)	20	Borderline personality disorder	Acute monotherapy	400-800mg/day	Placebo (n=10)	**At baseline:** **↓Stage N1:** in CBZ (5.67±2.07) vs. Placebo (9.63±3.38)** **After treatment:** **↑Stage N3(%):** in CBZ (4.95±2.39) vs. Baseline (2.38±2.63)**; **↑SWS(%):** in CBZ (11.81±10.63) vs. Baseline (4.14±5.17)**;
	Nayak et al (2016)	Cross-sectional case-control. (Class III)	40	Temporal-lobe epilepsy	Drug-naive (n=20) CBZ monotherapy (n=20)	NA	Healthy controls (n=40)	**↑TST (h):** in CBZ (8.50±0.58) vs. Controls (7.48±0.55)*** **↓SE(%):** in CBZ (76.38±12.23) vs. Controls (84.64±9.51)* **↓Stage N1 (%):**in CBZ (4.50±2.69) vs. Controls (8.07±4.22)* **↑REM arousal index:** in CBZ (9.30±7.39) vs. Controls (4.84±6.35)*** No significative differences in controls vs. drug-naïve patients
Phenobarbitone	**Prinz et al (1981)**	Prospective, non-randomized (Class III)	5	Healthy volunteers	Acute and chronic monotherapy	100mg	Placebo	**Acute:** significative differences vs. placebo **Chronic (1 month):** **↓Sleep latency (min):** in PB (3.40±0.87) vs. placebo (8.23±2.50) **↓ Stage N4 (%):** in PB (2.95±0.89) vs. placebo (9.36±1.98)
	Karacan et al (1981)	Double-blind, non-randomized, crossover (Class I)	24 (males only)	Healthy volunteers	Acute monotherapy	80, 140, 240mg	Placebo	**Results presented in (mean).** <u>80mg:</u> **↓No. of stage shifts:** in PB night 1 (34.5) vs. Placebo (39.4)* **↓Stage REM (%):** in PB night 1 (21.9) vs. Placebo (25.5)** **↑Stage N2(%):** in PB night 1 (61.0) vs. Placebo (56.1)* **↓No. of awakenings:** in PB night 2 (0.9) vs. Placebo (1.6)* **↑Latency to stage 0 (min):** in PB night 2 (305) vs. Placebo (205)* **↓Stage REM (%):** in PB night 2 (21.2) vs. Placebo (25.4)*** **↑Stage N2(%):** in PB night 2 (60.7) vs. Placebo (56.6)* <u>140mg:</u> **↓Stage REM (%):** in PB night 1 (18.9) vs. Placebo (25.5)*** **↑Stage N2(%):** in PB night 1 (62.1) vs. Placebo (56.1)** **↓REM episode duration (min):** in PB night 1 (22.4) vs. Placebo (26.3)* **cNo. of awakenings:** in PB night 2 (0.7) vs. Placebo (1.6)** **↑Latency to stage 0 (min):** in PB night 2 (301) vs. Placebo (205)* **↓Stage REM (%):** in PB night 2 (19.6) vs. Placebo (25.4)*** **↑Stage N2(%):** in PB night 2 (63.4) vs. Placebo (56.6)*** **↓REM episode duration (min):** in PB night 2 (21.4) vs. Placebo (27.9)*** <u>240mg:</u>

								↓No. of stage shifts: in PB night 1 (32.9)* vs. Placebo (39.4)** **↑Latency to REM (min):** in PB night 1 (148) vs. Placebo (85)*** **↓Stage REM (%):** in PB night 1 (16.1) vs. Placebo (25.5)*** **↑Stage N2(%):** in PB night 1 (66.3) vs. Placebo (56.1)*** **↓No. of REM episodes:** in PB night 1 (3.5) vs. Placebo (4.2)** **↓REM episode duration (min):** in PB night 1 (21.6) vs. Placebo (26.3)* **↓No. of awakenings:** in PB night 2 (0.2) vs. Placebo (1.6)*** **↓No. of stage shifts:** in PB night 2 (27.5)* vs. Placebo (34.8)** **↑Latency to stage N1 (min):** in PB night 2 (389) vs. Placebo (205)*** **↑Latency to REM (min):** in PB night 2 (171) vs. Placebo (98)*** **↓Stage REM (%):** in PB night 2 (15.8) vs. Placebo (25.4)*** **↑Stage N2(%):** in PB night 2 (67.4) vs. Placebo (56.6)*** **↓No. of REM episodes:** in PB night 2 (3.2) vs. Placebo (4.2)*** **↓REM episode duration (min):** in PB night 2 (21.8) vs. Placebo (27.9)**
Phenytoin	**Roder-Wanner et al (1987)**	Prospective longitudinal, non-blind (Class III)	31	Patients with new-onset epilepsy	Acute monotherapy	100mg	Placebo	Acute 100mg PHE in whole group (n=31): **↑Stage N4 (%):** in PHE (41.5±32.4) vs. placebo (29.1±27.3)* Acute 100mg PHE in group with generalized epilepsy (n=9): **↑Stage N4 (%):** in PHE (53.0±34.5) vs. placebo (36.8±29.5)** Acute 100mg PHE in group with focal epilepsy (n=8): **↓REM(%):** in PHE (17.1± 8.4) vs. placebo (26.7±12.9)* **After 4-6 weeks of PHE (check figure in paper for values):** **↓Sleep latency (min):** in PHE vs. Baseline* **↓Stage N1 (%):** in PHE vs. Baseline* **↓Stage N2 (%):** in PHE vs. Baseline* **↑SWS (%):** in PHE vs. Baseline* **↓REM(%):** in PHE vs. Baseline*
Valproic Acid	**Harding et al (1985)**	Prospective, single-blind (Class III)	10	Healthy adults	Acute monotherapy	2 days placebo, 2 days placebo + 500mg VPA, 14 days 1000mg VPA	Placebo	**Visual evocked potential (VEP) and EEG sleep recording:** **-No significative differences in VEP** **On sleep EEG:** (no values presented) **↓REM:** in high dose VPA vs. placebo*** **↓REM:** in high dose VPA vs. low dose*** **↓REM:** in low dose VPA vs. withdrawal*** **↑SWS:** in high dose VPA vs. placebo* **↑SWS:**in high dose VPA vs. low dose**
	Eisenser et al (2004)	Randomized, placebo-controlled, double-blind, cross-over study (Class I)	20	Idiopathic RLS	Acute monotherapy	300mg-SR In the first 2 days followed by 600mg-SR	Placebo And crossover with Levodopa	**↑Latency to stage N2:** In VPA-SR (40.6±28.8) vs. placebo (29.7±26.8);*

*Table IV Summary of papers on new antiepileptic drugs. (n=43). CLO: Clobazam; CNZ: Clonazepam; FEL: Felbamate; GBP: Gabapentin; LAC: Lacosamide; LTG: Lamotrigine; LEV: Levtiracetam; PMP: Perampanel; PGB: Pregabalin; TGB: Tiagabine; TPM: Topiramate; ZNS: Zonisamide. *: p<0,05; **: p>0,01; ***: p<0,001.*

	Authors	Type of study (class of evidence)	N	Population	Type of therapy (AED dose)	Dose (per day)	Comparison	Significative PSG Results (mean ± SD)
Clobazam	**Nicholson et al (1977)**	Prospective, Randomized, double-blind. (Class I)	6	Healthy adults	Single-dose (10mg or 20mg/day)	10mg, 20mg	Placebo and group with triflubazam	**Clobazam 10mg:** **↓Stage N1(%):** in CBZ (4.4±32) vs. Placebo (6.6±32)* **↓Sleep onset latency (min):** in CBZ (17.7±40) vs. Placebo (27.1±40)* **Clobazam 20mg:** **↓Stage N1(%):** in CBZ (4.3±32) vs. Placebo (6.6±32)* **↑Stage N2(%):** in CBZ (54.7±8) vs. Placebo (49.2±8)* **↓Stage N3(%):** in CBZ (7.7±19) vs. Placebo (11.2±19)** **↓SWS(%):** in CBZ (16.3±16) vs. Placebo (19.7±16)* **↓Sleep onset latency (min):** in CBZ (16.0±40) vs. Placebo (27.1±40)*
Clonazepam	**Saletu et al (2010)**	Single-blind, nonrandomized, crossover (Class III)	21	Drug-free adults with bruxism	Single-dose (1 mg/day)	1mg	Healthy controls and placebo	**↓No. of awakenings:** in CNZ (8.4±5.3) vs. Placebo (13.0±6.2)** **↓Awakening index (no/h of sleep):** in CNZ (1.2±0.8) vs. Placebo (2.4±1.3)** **↓WASO (min):** in CNZ (17.7±19.2) vs. Placebo (54.0±61.0)** **↑TST (min):** in CNZ (419.1±22.6) vs. Placebo (372.0±71.3)** **↑SE (%):** in CNZ (93.0±5.0) vs. Placebo (83.3±15.9)** **↓Stage N1 (%):** in CNZ (4.3±3.1) vs. Placebo (7.5±3.6)** **↑Stage N3(%):** in CNZ (9.0±5.3) vs. Placebo (7.1±3.8)** **↓Stage shift index (n/h of sleep):** in CNZ (17.5±4.4) vs. Placebo (21.0±5.1)**
	Ferri et al (2013)	Observational (Class III)	57	Idiopathic REM sleep behavior disorder (iREMSBD)	Chronic monotherapy	0.5-1.0 mg	iREMSBD taking bedtime clonazepam (n=15) Control: iREMSBD drug-free (n=42)	**Comparison between the two groups at baseline:** **↓Stage shifts (n/hour):** in CNZ (12.8±4.7) vs. Control (16.5±6.59)* **↑ SE (%):** in CNZ (83.6±6.99) vs. Control (76.0±13.08)* **↓WASO (%):** in CNZ (10.1±6.19) vs. Control (17.9±9.84)** **↓Stage N1 (%):** in CNZ (6.6±3.06) vs. Control (9.0±4.08)* **↑Stage N2 (%):** in CNZ (46.2±10.88) vs. Control (38.7±8.81)** There were no statistically significant differences in the first follow-up (2.6±1.08 years) of patients taking CNZ (n=13)
	Sakai (2016)	Randomized, double blind, crossover (class I)	19	Primary sleep bruxism	Acute monotherapy, crossover with clonidine	1mg	Placebo	**No significative differences in sleep parameters in CNZ vs. placebo.**
	Ferri et al (2017)	Observational (Class III)	64	Idiopathic REM sleep behavior disorder (iREMSBD)	Chronic monotherapy or acute monotherapy	0.5–2 mg	Drug-naïve (n=29) Chronic CNZ therapy (n=14) Healthy controls (n= 21)	**In chronic treatment patients (n=14) vs. drug naïve patients (n=29)** **↑Stage N2:** in chronic CNZ (44.6±9.14) vs. drug-naïve patients (38.5±8.53)* **In chronic treatment patients (n=14) vs. Controls (n=21)** **↓Awakenings (/hour):** in chronic CNZ (4.0±2.32) vs. controls (7.2±2.9)* **↑SE (%):** in chronic CNZ (83.5±7.85) vs. controls (68.3±12.55)**

								↑SWS (%): in chronic CNZ (17.5±6.75) vs. controls (10.4±7.82)***
Felbamate	**Marciani et al (1998)**	Case report (Class IV)	1	Lennox-Gastaut syndrome	Acute add-on therapy	1800mg	NA	**After 4 months:** **↓Phase shifts:** in FEL (21.4) vs. Baseline (41.8) **↓No. of Awakenings:** in FEL (17) vs. Baseline (43) **↓Stage N1 (%):** in FEL (39.9) vs. Baseline (54.5) **↓WASO(%):** in FEL (16) vs. Baseline (18.6)
Gabapentin	**Rao et al (1988)**	Double blind, placebo-controlled, randomized crossover (Class I)	6	Healthy adults	Acute monotherapy	1st day: placebo 2nd day: GBP 300mg 3rd day: GBP 600mg	Placebo	**↓deep sleep latency:** in GBP was decreased to 70% vs. controls * **↑SWS:** was increased to 120% in GBP vs. controls.*
	Placidi et al (2000)	Prospective, nonrandomized (Class III)	18	Drug resistant epilepsy Focal cryptogenic (n=12) Focal symptomatic (n=6)	Acute add-on therapy	1800-2400mg/day	NA	**4-months vs. Baseliine:** **↓Stage N1:** in GBP (9.7±4.2) vs. Baseline. (14.4±3.2)*** **↑SWS(%):** in GBP (17.1±6.5) vs. Baseline. (14.4±5.0)* **↑REM(%):** in GBP (14.7±5.5) vs. Baseline. (11.1±3.1)*** **↓No. of awakenings:** in GBP (13.9±7.4) vs. Baseline. (21.6±11.0)***
	Foldvary-Schaefer et al (2002)	Prospective, non-randomized, open label (Class III)	19	Healthy adults	Acute monotherapy	300-1800mg	Healthy controls (n=9)	**GBP group (n=10):** **↑SWS(%):** in GBP (13.0±0.07) vs. Baseline. (8.0±0.05)**
	Lo et al (2010)	Open-label (Class IV)	18	Primary insomnia	Acute monotherapy	Mean dose = 540mg (200-900mg)	NA	**After 4 weeks of GBP treatment:** **↑ SE (%):** in GBP (87.17±11.37) vs. baseline (80.00±14.79)* **↓ WASO (min):** in GBP (7.84±9.92) vs. Placebo (16.45±14.78)* **↑ SWS (%):** in GBP (17.68±9.88) vs. baseline (10.47±9.86)***
	Madani et al (2012)	Single-blind, randomized clinical trial (Class II)	20 GBP group (n=10)	PSG docunted sleep bruxism	Acute monotherapy	100mg during 3 nights 200mg the next 3 nights 300mg from the 6th week to 2 months	Stabilization splint	**Before treatment:** **↑ stage N3 (%)** in GBP (18.1±2.6) vs. splint group (15.7±2.5) at baseline **Versus Baseline:** **↑ TST (min):** in GBP (441.7±45.0) vs. baseline (382±40.9) **↓ NREM Sleep latency (min):** in GBP (10.9±9.9) vs. baseline (24.2±14.1) **↑ SWS (%):** in GBP (20.9±4.0) vs. baseline (18.1±2.6) **↑ SE (%):** in GBP (93.1±3.9) vs. baseline (86.3±4.8)

	Furey et al (2014)	5-hour sleep advance, randomized, double-Blind, placebo-Controlled, Multicenter (Class I)	237	Adults with sleep complaints	Acute monotherapy	250mg	Placebo (n=115)	Gabapentin (n=122) Day 1: **↑TST (min):** in GBP (347.6±7.5) vs. Placebo (283.9±9.8)*** **↓ WASO (min):** in GBP (107.0±7.3) vs. Placebo (149.1±9.6)** **↓Stage N1 (%):** in GBP (12.3±0.6) vs. placebo (15.7±1.1)* Day 28: **↑TST (min):** **↓ WASO (min):** in GBP (113.6±8.1) vs. placebo (152.3±9.3)** **↑REM (%):** in GBP (15.6±0.5) vs. placebo (13.6±0.6)*
	Rosenberg et al (2014)	Randomised, double-blind, multicenter clinical trial (Class I)	Placebo (n=124) 250mg (n=124) 500mg (n=125)	Adults with sleep complaints	Acute monotherapy	250 or 500mg groups	Placebo	**↑TST (min):** in 500mg (378.7±7.3)*** or 250mg (356.5±7.3)*** vs. placebo (311.4±8.4) **↓ WASO (min):** in 500mg (73.2±5.8)*** or 250mg (100.7±6.6)*** vs. placebo (135.7±7.0) **↓ Stage N1 (min)**: in 500mg (10.8±0.7)*** or 250mg (11.8±0.7)*** vs. placebo (15.1±1.0) **↑SWS (%)** in 500mg (17.0±1.1)*** or 250mg (15.4±1.0)* vs. placebo (12.6±0.9)
	Piovezan et al (2017)	double-blind, randomized, placebo-controlled cross-over pilot study (Class II)	8	Healthy men (≥60 years old)	Acute monotherapy	300mg	Placebo	No significative changes in objective sleep parameters were found
Lacosamide	**Hudson et al (2015)**	Multicenter, interventional, open-label study (Class III)	25	Healhty adults	Monotherapy	300mg	NA	No significative changes in objective sleep parameters were found
	Foldvary-Schaefer et al (2017)	Phase IV randomized, controlled, double blind, single center trial (Class I)	52	Focal epilepsy	Acute adjunctive	400mg	Placebo (n=10)	**Comparison between LAC (n=42) and placebo (n=10) at baseline** **↓Arousal Index:** in LAC [6.1(4.9-8.4)] vs. Placebo [10.3 (7.0-13.7)]* **Comparison between LAC (n=35) and baseline at follow-up** **↓Arousal Index:** in LAC −5.0 [−14.0, 3.0] vs. Baseline.* values expressed in Median (P25-P75)
Lamotrigine	**Placidi et al (2000)**	Prospective, uncontrolled, non-randomized (Class III)	13	Drug-resistant focal epilepsy	Acute adjunctive	200mg	NA	**↑REM (%):** in LTG (13.3±6.0) vs. Baseline (8.5±4.3)** **↓SWS (%):** in LTG (12.4±6.0) vs. Baseline (17.8±6.1)* **↓No. of entries in REM:** in LTG (36.0±27.0) vs. Baseline (16.0±12.0);* **↓ No. of phase shifts:** in LTG (38.0±11) vs. Baseline (32.0±11.0)*

	Foldvary et al (2001)	Prospective, uncontrolled, non-randomized (Class III)	10	Focal epilepsy	Acute adjunctive Chronic monotherapy: CBZ (n=7); PHT (n=3)	400mg	NA	**↑Stage N2 (%):** in LTG (57.5) vs. Baseline (50.9).* **↓SWS (%):** in LTG (13.0) vs. Baseline (20.2).* Authors did not present standard deviation. Results in (mean)
Levetiracetam	**Bell et al (2002)**	Double-blind, randomized crossover (Class I)	N=12 volunteers N= 16 patients	Study 1: healthy volunteers Study 2: focal epilepsy on carbamazepine monotherapy	Adjunctive	1000mg	Placebo	Study 1 (n=12): **↑ Stage N2 (min):** on LEV (270.0±34.2) vs. Placebo (235.0±45.5); **↑ REM latency (min):** on LEV (121.3±70.0) vs. Placebo (69.8±); Study 2 (n=16): **↑ Stage N2 (min):** on LEV (231.0±33.6) vs. Placebo (174.0±21.9); **↓ Stage N4 (min):** on LEV (58.0±30.1) vs. Placebo (72.0±27.2);
	Bazil et al (2005)	Randomised prospective (Class II)	12	Healthy	Monotherapy	3 days 500mg, 3 days 1000mg, 3 days 1500mg and 3days 2000mg	Placebo	**↑ No. Of awakenings** in follow-up LVT (17.00±1.60) vs. Placebo (8.00±1.80)*
	Cicolin et al (2006)	Double-blind crossover (Class I)	14	Healthy volunteers	Acute monotherapy	Up to 2000mg/day	Placebo	**↑TST (min):** in LEV (391.44±30.58) vs. Placebo (363.72±40.04)** **↑SE (%):** in LEV (92.78±1.10) vs. Placebo (90.61±1.47)** **↑Stage N2 (min):** in LEV (253.09±23.61) vs. Placebo (228.22±30.02)*** **↑Stage N4 (min):** in LEV (23.18±3.58) vs. Placebo (16.28±3.91)*** **↓ WASO (min):** in LEV (12.71±1.44) vs. Placebo (18.00±4.76)** **↑Stage N2 (%):** in LEV (64.67±3.66) vs. Placebo (62.71±3.83)*** **↑Stage N4 (%):** in LEV (5.92±0.77) vs. Placebo (4.47±0.89)*** **↓REM(%):** in LEV (14.99±2.59) vs. Placebo (17.55±3.59)** **↓ WASO (%):** in LEV (3.26±0.39) vs. Placebo (4.97±1.24)** **↓Stage shifts (No.):** in LEV (66.00±4.42) vs. Placebo (73.50±7.01)*** **MSLT:** No significant changes were detected.
	Yilmaz et al (2007)	Prospective, non-randomized (Class III)	22	Complex focal epilepsy	Chronic monotherapy (n=10) Chronic add-on therapy (n=12)	2000mg/day	Control group (n=20)	**Measured by actigraphy and MWT** **After 3 weeks of LEV monotherapy:** **↓Total activity score (no./night):** in LEV (7779±7861) vs. Baseline (9840±7323)** **↑Daytime napping episodes (no./day):** in LEV (3.45±1.80) vs. Baseline (2.44±0.42)** **↑Total nap duration (min/day):** in LEV (38.00±8.23) vs. Baseline (23.00±3.90)** **After 3 weeks of LEV as add-on:**

								↓**Total activity score (number/night):** in LEV (5980±8200) vs. Baseline (9840±7323)* ↑**Daytime napping episodes (no./day):** in LEV (6.70±1.20) vs. Baseline (2.44±0.42)* ↑**Total nap duration (min/day):** in LEV (59.00±9.32) vs. Baseline (23.00±3.90)*
	Zhou et al (2012)	Observational prospective (Class III)	20	Focal epilepsy without sleep disorders	Monotherapy (n=4) Adjunctive (n=6)	1000mg/day	Healthy volunteer controls (n=10)	**1 week LEV (n=10) vs. Controls (n=10):** ↑ **REM latency (min):** in LEV (176.94±94.43) vs. Controls (98.75±60.97)* **1 week LEV (n=10) vs. Baseline (n=10):** ↓ **REM (min):** in LEV (59.55±33.27) vs. Baseline (71.45±37.12)* ↓ **REM (%):** in LEV (13.29±6.80) vs. Baseline (15.67±7.26)* **MSLT:** No significant changes were detected.
Perampanel	**González-Cuevas et al (2016)**	Prospective, non-interventional (Class III)	10	Focal epilepsy	Adjunctive	4mg	NA	**MWT (n=10) :** No statistically significant differences were found in objective sleep parameters.
	Garcia-Borreguero et al (2017)	Prospective, open trial (Class III)	20	Idiopathic RLS	Monotherapy	2mg (increased to 4mg in week 4 if necessary) Mean: 3.8mg/day	NA	↑**TST (min):** in PMP (364.64±44.42) vs. Baseline (329.85±39.30)* ↓**Sleep latency (min):** in PMP (20.68±5.10) vs. Baseline (32.60±13.10)* ↑**Sleep efficiency(%):** in PMP (85.64±5.22) vs. Baseline (73.02±7.43)*** ↓**WASO (min):** in PMP (39.99±19.41) vs. Baseline (89.25±26.12)*** ↑**Arousal Index:** in PMP (25.06±6.33) vs. Baseline (37.29±12.58)** ↓ **Stage N1 (min)**: in PMP (57.59±19.46) vs. Baseline (73.10±19.86)* ↑ **Stage N3 (min)**: in PMP (52.00±10.94) vs. Baseline (29.45±18.40)** ↓ **Stage N1 (%)**: in PMP (16.13±5.66) vs. Baseline (22.40±6.44)** ↑ **Stage N3 (%)**: in PMP (14.40±3.04) vs. Baseline (8.90±5.45)** ↓**REM latency (min):** in PMP (86.55±20.72) vs. Baseline (115.20±36.65)** ↓**PLM:** in PMP (2.53±0.85) vs. Baseline (3.03±0.86)* ↓**PLM index:** in PMP (4.36±2.00) vs. Baseline (27.76±6.75)***
	Hindmarch et al (2005)	Randomized, double-blind, placebo and active-controlled, 3-way crossover (Class I)	24	Healthy adults	Acute monotheraphy	450 mg	Placebo and Alprazolam	**<u>Means of nights 2, 3, 4:</u>** ↓**SL (min):** in PGB (6.83±5.55) vs. placebo (13.95±10.78) ↑**SE (%):** in PGB (96.11±2.13) vs. placebo (90.62±5.07) ↑**TST (min):** in PGB (461.73±10.22) vs. placebo (435.55±24.39) ↓**No. of awakenings (<1min):** in PGB (7.88±4.43) vs. placebo (17.45±6.38) ↓**No of awakenings (>1min):** in PGB (1.30±1.50) vs. placebo (3.84±3.34) ↑**SWS (%) in 1st third:** in PGB (66.63±10.35) vs. placebo (46.65±12.97) ↑**SWS(%) in 2nd third:** in PGB (31.11±14.89) vs. placebo (19.64±10.04) ↑**SWS(%) in 3rd third:** in PGB (16.92±10.8) vs. placebo (10.8±8.61)
	de Haas et al (2007)	Randomised, double-blind, placebo-controlled. (Class II)	15 (PGB n=8)	Focal epilepsy + subjective sleep disturbance	Adjunctive	300mg	Placebo (n=7)	**<u>After 4 weeks, in-home PSG:</u>** ↓**No. of awakenings:** in PGB (2.8±5.1) vs. Placebo (5.4±3.5)* ↑**Sleep efficiency (%):** in PGB (87.1±8.9) vs. Baseline (80.6±13.6)** ↓**WASO (min):** in PGB (15.1±29.5) vs. Baseline (50.5±41.6)* ↓**No. of awakenings:** in PGB (2.8±5.1) vs. Baseline (6.0±4.6)*

Pregablin								
	Romigi et al (2009)	Prospective, single-blind, uncontrolled (Class III)	12	Focal epilepsy	Adjunctive	Individualized (150-375 mg/day)	NA	**<u>After 3-months of PGB:</u>** **↓Stage 2 (%):** in PGB (54.08 ± 12.21) vs. Baseline (60.44±7.34); **↑ REM(%):** in PGB (16.57±7.43) vs. Baseline (10.58±6.44).
	Garcia-Borreguero et al (2010)	Randomized, double-blind, placebo-controlled (Class I)	58	Idiopathic RLS	Acute monotheraphy	Mean dose: 337mg/day	Placebo (n=28)	**<u>PGB (n=30) on week 12:</u>** **↑SE:** in PGB (85.67±15.42) vs.Baseline (77.71±16.67) vs. Placebo (75.76±19.88)*** **↓WASO:** in PGB (27.18±24.16) vs.Baseline (54.71±36.32) vs. Placebo (73.46±63.17)** **↑Stage N3:** in PGB (60.62±55.16) vs.Baseline (46.29±35.83) vs. Placebo (35.23±27.01)* **↑Stage N4:** in PGB (56.04±49.34) vs.Baseline (38.79±35.72) vs. Placebo (39.78±35.37)***
	Bazil et al (2012)	Prospective, Randomised, double-blind, crossover (Class II)	9	Focal epilepsy + insomnia	Adjunctive	300mg	Placebo	↑**SWS** increased with PGB 4.1±2.5% vs. Baseline, compared with a drop with placebo of 2.0±1.8% vs. Baseline* **↓Stage N1:** check figure in reference for details.*
	Roth et al (2012)	Randomized, double-blind, placebo-controlled, 2-treatment, 2-period, crossover (Class I)	102	Fibromyalgia + sleep disturbance	Acute monotheraphy	300-450 mg/day	Placebo	**<u>After 8 weeks PGB:</u>** **↑TST (min):** in PGB (396.2±4.7) vs. Placebo (370.6±4.7)** **↓WASO (min):** in PGB (51.5±3.8) vs. Placebo (70.7±3.8)*** **↓Sleep latency (min):** in PGB (34.5±3.7) vs. Placebo (41.6±3.7)* **↑SE (%):** in PGB (82.6±0.98) vs. Placebo (77.2±0.97)*** **↑SWS (%):** in PGB (17.2±1.0) vs. Placebo (15.0±1.0)***
	Garcia-Borreguero et al (2013)	Randomizes, double-blind, 3-way crossover (Class II)	75	RLS	Acute monotherapy	300mg	Placebo and Pramipexole	**<u>After 4 weeks of PGB:</u>** **↓WASO (min):** in PGB (51.5±4.2) vs. Placebo (78.6±4.2)*** **↓PLMAI, PLMA/hour:** in PGB (3.9±0.7) vs. Placebo (7.6±0.7)***
Tiagabine	**Mathias et al (2001)**	Double-blind, prospective (Class I)	10	Healthy adults	Monotherapy	5mg	Placebo	**↑SWS(%):** in TGB (62.9±33.5) vs. Placebo (32.8±20.0)* **↑Sleep efficiency (%):** in TGB (82.2±4.2) vs. Placebo (78.1±5.7)*
	Walsh et al (2005)	Randomized, double-blind, Latin-square design. (Class I)	22	Healthy elderly	Monotherapy	2, 4 and 8 mg	Placebo	**2mg:** no statistically significative differences were found vs placebo **4mg:** **↑TST (min):** in TGB (407.7±33.4) vs. placebo (396.0±31.0)* **↓WASO (min):** in TGB (64.9±31.8) vs. placebo (77.2±31.9)* **↑SWS (min):** in TGB (59.7±39.1) vs. placebo (44.5±36.8)* **8mg:** **↓Stage N1 (min):** in TGB (62.4±31.6) vs. placebo (81.3±34.6)***

								↑SWS (min): in TGB (87.0±61.0) vs. placebo (44.5±36.8)*** **↓REM (min):** in TGB (58.4±18.1) vs. placebo (68.3±16.6)** **↓SWS latency (min):** in TGB (33.1±25.8) vs. placebo (51.0±35.3)** **↓REM latency (min):** in TGB (94.2±48.2) vs. placebo (71.8±30.2)**
	Walsh et al (2006)	Double-blind, randomized, parallel-group, dose-response study (class I)	230	Primary insomnia	Monotherapy	4, 6, 8 and 10 mg	Placebo (n=47)	**4mg (n=46):** **↓Stage N1 (%):** in TGB (33.6±19.0) vs. Baseline (39.3±22.5)** **6mg (n=45):** **↓Stage N1 (%):** in TGB (25.6±16.8) vs. Baseline (32.7±18.0)*** **8mg (n=45):** **↓Stage N1 (%):** in TGB (27.2±18.2) vs. Baseline (32.7±18.0)*** **10mg (n=47):** **Significance is in change from baseline vs. placebo.**
	Walsh et al (2006)	Double-blind, randomized, five-period, latin square, crossover (Class I)	50	Primary insomnia	Monotherapy	4, 8, 12 and 16 mg	Placebo	**4 mg (n=50):** **↑SWS(%):** in TGB (10.2±1.3) vs. placebo (5.7±1.3)* **↓REM(%):** in TGB (18.5±0.6) vs. placebo (20.2±0.6)* **8mg (n=50):** **↓Stage N1 (%):** in TGB (8.2±0.6) vs. placebo (11.0±0.6)** **↑SWS(%):** in TGB (13.1±1.3) vs. placebo (5.7±1.3)* **↓REM(%):** in TGB (16.8±0.6) vs. placebo (20.2±0.6)*** **12mg (n=50):** **↓Stage N1 (%):** in TGB (7.3±0.6) vs. placebo (11.0±0.6)*** **↓Stage N2 (%):** in TGB (58.9±1.1) vs. placebo (63.2±1.1)** **↑SWS(%):** in TGB (20.0±1.3) vs. placebo (5.7±1.3)*** **↓REM(%):** in TGB (13.8±0.6) vs. placebo (20.2±0.6)*** **16 mg (n=50):** **↓WASO (min):** in TGB (55.9±3.9) vs. placebo (66.9±3.9)* **↓Stage N1 (%):** in TGB (7.8±0.6) vs. placebo (11.0±0.6)* **↓Stage N2 (%):** in TGB (53.6±1.1) vs. placebo (63.2±1.1)*** **↑SWS(%):** in TGB (27.5±1.3) vs. placebo (5.7±1.3)*** **↓REM(%):** in TGB (11.1±0.6) vs. placebo (20.2±0.6)*
	Walsh et al (2006)	Radomized, double-blind, parallel-groups (Class I)	38	Healthy volunteers	Monotherapy	8mg	Placebo	**Night 2 versus mean of nights 3-6** **↑SWS:** More [29.1 (± 23.8)] minutes of SWS on nights 3 to 6 compared to baseline vs. placebo [5.4 (± 22.1)] fewer minutes compared to baseline.

	Roth et al (2006)	Radomized, double-blind, parallel-groups (Class I)	207	Elderly with primary insomnia	Monotherapy	2, 4, 6, 8 mg	Placebo (n=38)	**2mg (n=42):** no significative changes from baseline vs. placebo **4mg (n=38):** **↓Stage N1 (min):** in TGB (31.2±2.8) vs. placebo (39.1±3.1)* **↑SWS(min):** in TGB (44.2±5.6) vs. placebo (35.2±4.4)* **6mg (n=45):** **↓Stage N1 (min):** in TGB (29.7±2.6) vs. placebo (39.1±3.1)* **↑SWS(min):** in TGB (72.2±7.9) vs. placebo (35.2±4.4)* **↓REM (min):** in TGB (50.6±3.0) vs. placebo (63.7±2.9)* **↓No. 30s-awakenings:** in TGB (30.6±1.3) vs. placebo (35.4±1.8)* **↑Ratio SWS/(Stage N1+WASO) (%)::** in TGB (0.9±0.21) vs. placebo (0.3±0.005)* **8mg (n=41):** **↓Stage N1 (min):** in TGB (30.5±3.2) vs. placebo (39.1±3.1)* **↑SWS(min):** in TGB (70.0±8.3) vs. placebo (35.2±4.4)* **↓REM (min):** in TGB (44.5±3.8) vs. placebo (63.7±2.9)* **↓No. 30s-awakenings:** in TGB (32.2±1.8) vs. placebo (35.4±1.8)* **↑Ratio SWS/(Stage 1+WASO) (%)::** in TGB (0.6±0.1) vs. placebo (0.3±0.005)*
	Feld et al (2013)	Randomised, double-blind, crossover (Class I)	12	Healthy adults (only men)	Monotherapy	10mg	Placebo	**↓Stage N1 (%):** in TGB (4.23±1.16) vs. placebo (8.44±1.08) ** **↑SWS (%):** in TGB (24.30±3.34) vs. placebo (17.51±0.89); ** **↓REM(%):** in TGB (12.37±2.14) vs. Placebo (17.51±0.89) *
	Taranto-Montemurro et al (2017)	placebo-controlled, double-blind, crossover trial (Class I)	12	Obstructive apnea	Monotherapy	12mg	Placebo	No significative differences were found vs. placebo.
Topiramate	**Bonnani et al (2004)**	Prospective, non-randomized, non-blind (Class III)	14	Focal epilepsy	Monotherapy	200 mg/day	14 healthy controls	**After 2 months of TPM:** Sleep parameters in PSG reported no significative changes. MSLT scores did not significantly change in patients as compared with pretreatment values.
Zonisamide	**Romigi et al (2013)**	Open-label prospective (Class III)	Baseline (n=12) Follow-up 3 months (n=12)	Focal epilepsy	Adjunctive	200-300 mg/day	NA	↑ **No. Of awakenings** in ZNS (12.72±10.65) vs. Baseline (9.55±5.65)*
	Eskandari et al (2014)	Randomised, double-blind, parallel study with open extension phase (Class II)	47 (ZSM, n=22)	OSA	Adjunctive	300mg	NA	**Sleep-related variables at 4 weeks:** No significative changes

*Table V Summary of papers on more than one antiepileptic drug (n=7).PB: Phenobarbitone; PHE: Phenytoin; ETH: Ethosuximide; VPA: Valproic acid; CNZ: Clonazepam; CBZ: Carbamazepine; GBP: Gabapentin; LTG: Lamotrigine; FBM: Felbamate; ZNS: Zonisamide; TGB: Tiagabine; CBZ-CR: Carbamazepine- controlled release. *: p<0,05; **: p>0,01; ***: p<0,001.*

Study	Type of study (class of evidence)	N	Population	AEDs studied (N)	Type of therapy	Dose (per day)	Comparison	Significative PSG Results (mean ± SD)
Wolf et al (1984)	Prospective, non-blind, non-randomised (Class III)	40	Focal epilepsy (n=15) Generalized epilepsy (n=17)	PB (n=34) PHE (n=31)	PHB monotherapy. 4 cycles and Crossover with PHE	Daily dose. Steady-state serum level PB=26.8 µg/ml (10-46) PHE= 17.1 µg/ml (7-40)	Placebo	Phenobarbitone (n=34) and Phenytoin (n=34): 1st Cycle: ↑**REM (min):** in PB (126.4±44.9) vs. Baseline (95.3±39.7)* ↑ **REM latency (min):** in PB (112.9±40.6) vs. Baseline (81.7±33.8)* ↑ **Stage N4 (min):** in PB (45.1±30.1) vs. Baseline (25.4±13.5)* 2nd Cycle: ↓**Time awake (min):** in PB (1.7±2.0) vs. Baseline (4.6±8.6)* ↑**REM (min):** in PB (117.1±21.9) vs. Baseline (108.1±25.6)** ↑ **REM latency (min):** in PB (220.8±50.2) vs. Baseline (175.5±50.6)** ↑**Stage N2 (min):** in PB (58.5±25.3) vs. Baseline (38.7±15.7)* ↑**Stage N3 (min):** in PB (32.0±19.1) vs. Baseline (22.5±14.4)** ↓**Stage N4 (min):** in PB (13.3±7.4) vs. Baseline (21.2±16.6)** 3rd Cycle: ↓**Time awake (min):** in PB (1.8±2.6) vs. Baseline (3.8±3.0)** ↓**Stage N4 (min):** in PB (3.5±7.4) vs. Baseline (8.0±10.3)** ↑ **REM latency (min):** in PB (281.8±48.2) vs. Baseline (321.9±52.1)** ↓**Stage N1 (min):** in PHE (4.0±3.9) vs. Baseline (8.7±6.8)* ↓**Stage N2 (min):** in PHE (41.9±17.3) vs. Baseline (54.9±17.4)** ↑**Stage N3 (min):** in PHE (14.4±10.3) vs. Baseline (9.9±10.6)** ↑**Stage N4 (min):** in PHE (17.7±15.3) vs. Baseline (8.0±10.3)* 4th Cycle: ↓**Time awake (min):** in PB (1.3±0.8) vs. Baseline (3.2±4.0)* ↑ **REM latency (min):** in PB (403.1±50.7) vs. Baseline (366.1±47.9)** ↑**Stage N2 (min):** in PB (51.5±17.3) vs. Baseline (41.8±14.1)* ↑**Stage N3 (min):** in PB (36.9±18.3) vs. Baseline (26.4±12.8)** ↓**Stage N4 (min):** in PB (1.6±3.6) vs. Baseline (6.2±10.6)** ↑**Stage N3 (min):** in PHE (11.5±8.3) vs. Baseline (7.8±10.1)*
Wolf et al (1984)	Observational, non-randomized (Class III)	229	Absence seizures	ETH (n=143) VPA (n=187)	Monotherapy	NA	NA	**No values available** ↑**Stage N1 (%):** in ETH vs. Baseline* ↓**SWS (%):** in ETH vs. Baseline* ↑**REM duration (min):** in ETH vs. Baseline in third REM cycle * ↓ **REM duration (min):** in ETH vs. Baseline in fourth REM cycle *

								↑Stage N1 (%): in VPA vs. Baseline*
Drake et al (1990)	Observational (Class III)	17	Focal or generalized epilepsy	PHE (n=5), CBZ (n=5), VPA (n=5), CNZ (n=2)	Chronic Monotherapy	NA	NA	PHE (n=5), CBZ (n=5), VPA (n=5), CNZ (n=2) **↓SWS and REM:** in both groups compared to published norms but none values were presented.
Manni et al 1993	Observational (Class III)	30	Generalized epilepsy tretated with PB; Focal epilepsy treated with VPA;	PB (n=10) VPA (n=10)	Chronic monotherapy	PB (mean serum = 19.3±1.7µg/ml) VPA (mean serum = 85.7±4.7µg/ml)	Healthy controls (n=10)	MSLT: **↑Daytime sleep propensity:** in PB vs. controls and vs. CBZ **No significative differences in PSG recordings among the 3 groups.**
Bonanni et al (1997)	Prospective, nonrandomized (Class III)	26	Focal epilepsy	CBZ = 26 CBZ+VGB= 14	Chronic CBZ monotherapy (n=26) CBZ + VGB (n=14)	CBZ: 600-1600 mg VBB: 2-3 g/day	Healthy controls (n=12)	No significative differences were found
Legros et al (2003)	Observational, uncontrolled. (Class III)	39	Focal epilepsy with at least 24-h seizure-free		Monotherapy	Each drug with different dose	Patients with no AED as controls (n=13)	**PHE (n=7):** **↑Stage N1 (%):** in PHE (13.2±7.3) v. controls (7.7±4.8)**; **↓ SWS (%):** in PHE (7.9±4.2) v. controls (11.3±4.4)*; **↓REM (%):**in PHE (13.9±6.2) v. controls (18.8±5.1)*; **VPA (n=2):** **↑Stage N1 (%):** in VPA (16.8±9.8) v. controls (7.7±4.8)**; No significative differences were found in **CBZ (n=10), PB (n=1), GBP (n=3), LTG (n=4), PRI (n=1), FBM (n=1), ZNS (n=1), TGB (n=1).**
Cho et al (2011)	Longitudinal randomized trial. (Class II)	31	Newly diagnosed focal epilepsy	LEV (n=16) CBZ-CR (n=15)	Monotherapy	LEV (1000mg/day) CBZ-CR (400mg/day)	NA	**LEV group (n=16)** **↑ Sleep efficiency (min):** on LEV (90.62±4.77) vs. Baseline (84.32±13.65)*; **↓ WASO (min):** on LEV (31.72±38.88) vs. Baseline (55.61±56.06)*; **CBZ-CR group (n=15)** **↑Stage N3 (%):** on CBZ-CR (26.78±9.47) vs. Baseline (21.29±9.76)*;

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