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Effects of Four Antiepileptic Drugs on Sleep and Waking in the Rat Under both Light and Dark Phases

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BERTORELLI, R., N. FERRI, M. ADAMI AND E. ONGINI. *Effects of four antiepileptic drugs on sleep and waking in the rat under both light and dark phases.* PHARMACOL BIOCHEM BEHAV 53(3) 559–565, 1996.—Sedation is a common side effect of anticonvulsant drug therapy. To find out whether the new antiepileptic drugs, felbamate and lamotrigine, are able to produce sedation, we carried out electroencephalographic (EEG) studies in the rat to measure drug effects on sleep-wake patterns, during both light and dark phases. For comparison, the reference drugs, carbamazepine and phenobarbital, were also studied. EEG activity was recorded for 6 h after oral (PO) administration of drugs or vehicle, and the stages of wakefulness, rapid eye movements (REM) sleep and non-REM sleep were classified thereafter. In the light phase, felbamate (30–300 mg/kg) did not produce sedative effects, while lamotrigine (3–30 mg/kg) increased wakefulness at each dose tested. Carbamazepine (10–100 mg/kg) did not produce sleep-wake alterations, and phenobarbital (100 mg/kg) markedly suppressed REM. In the dark phase, felbamate (300 mg/kg), lamotrigine (30 mg/kg), and carbamazepine (100 mg/kg) reduced REM but did not change the total amount of sleep. Phenobarbital, at 100 mg/kg, markedly increased total sleep and greatly reduced REM. This study shows that the anticonvulsant drugs examined have different effects on the states of sleep and wakefulness in the rat. The data are discussed on the basis of the mechanism of action that characterizes each individual drug.

Anticonvulsant drugs Felbamate Lamotrigine Carbamazepine Phenobarbital Sleep-wake cycle Rat

A CRITICAL aspect of antiepileptic therapy is the occurrence of adverse effects. The ideal antiepileptic would prevent seizures compromising the patient's quality of life. The most common complaints following administration of antiepileptic drugs involve gastrointestinal and central nervous system (CNS) effects. The majority of neurological side effects are related to sleep disorders; that is, somnolence and insomnia, mood and behavior problems, headache, diplopia, and dizziness (21).

Because sedation is a common side effect of the drugs currently used, we designed a study based on the electroencephalographic (EEG) technique, to assess the effects of anticonvulsant agents on the sleep-waking cycle in the rat. The drugs, two new (felbamate and lamotrigine) and two established (carbamazepine and phenobarbital), differ in chemical nature and mechanism of action. Felbamate is an effective antiepileptic drug for treatment of epilepsy (30), which has efficacy in some forms of refractory partial epilepsy (17,35) and in the Lennox-Gastaut syndrome (10). Recently, because of some cases of serious hematologic disorders associated with chronic administration, use of felbamate has been limited in some countries. However, the drug has a unique spectrum of activity in patients refractory to other drug treatment and it possesses an interesting profile regarding mechanism of action. Felbamate is a dicarbamate, structurally related to meprobamate, which has been found to be potent in animal models of epilepsy and appears to interact with neurotransmission mediated by excitatory aminoacids (7,24). Lamotrigine is a drug of the new generation of antiepileptics which is effective for partial and secondary generalized tonic-clonic seizures (3). Lamotrigine is a triazine derivative chemically unrelated to any other current antiepileptic drug, while its antiepileptic profile is similar to that of carbamazepine and phenytoin (12). Its activity seems to depend upon inhibition of glutamate release (16), but interaction with sodium channels has been demonstrated in mouse neuroblastoma cell studies (15). Carbamazepine, a classic anti-

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convulsant drug possessing a wide spectrum of activity, is an iminostilbene structurally similar to the tricyclic antidepressant drug imipramine. It has been shown to be effective in the treatment of simple and complex partial and generalized tonic-clonic seizures but it is ineffective against generalized absence seizures (18). Carbamazepine most likely exerts its anticonvulsant activity by inhibiting voltage-dependent sodium channels (19). In addition, we assessed the effects of phenobarbital, an established antiepileptic drug which is known to induce marked sedative effects. Although it has been replaced by newer drugs as first choice treatment, it retains an important role as supplementary or alternative therapy. The mode of action of phenobarbital is believed to occur primarily through the enhancement of GABA-mediated inhibitory response (36). Because sleep-inducing effects of sedative-hypnotic drugs are difficult to demonstrate in the rat because this animal species spends more than half of the time sleeping (40), we studied drug effects under two different experimental conditions. In the first series of experiments, anticonvulsant drugs were administered during the light period, when sleep behavior is predominant. In the second series, the antiepileptic drugs were studied during the dark period, when rats are more active and the amount of sleep is reduced (11).

METHODS

Experimental Design During the Light Phase

Male Sprague–Dawley rats (Charles River, Calco, Italy) weighing 250–350 g, were maintained for one week on a 12-h light/12-h dark schedule (lights on at 7:00 a.m.) with free access to food and water before surgery, under standard conditions of humidity (50%) and room temperature (22°C). Procedures involving animals and their care were conducted in conformity with the institutional guidelines, in compliance with national and international laws and policies.

Electrodes for polygraphic recording of the EEG activity were implanted under anesthesia (equitensin, 1% pentobarbital, 4% chloral hydrate). The electrodes, which consisted of stainless-steel bars of 1 mm diameter, were threaded into the skull above the fronto-parietal (2 mm lateral and 2 mm posterior to bregma) and occipital (1 mm lateral and 2 mm anterior to lambda) cortex for recording EEG activity. Two reference electrodes were implanted over the cerebellar region. The rats were then housed singly in vertical Plexiglas cylinders (40 × 40 cm) and were allowed to recover for 1 week during which they were accustomed to being handled and to the cable system for EEG recording, to minimize the stress involved in the experimental procedures.

On the day of the experiment, the electrodes were connected to an electroencephalograph (Battaglia Rangoni, Casalecchio di Reno, Italy) by means of a cable system including a swivel device that allowed the animals to move almost freely. Polygraphic recordings were made from 9:00 a.m. to 3:00 p.m. and vehicle or antiepileptic drugs were administered at 8:45 a.m.

The recordings were evaluated visually and classified as wakefulness, rapid eye movement (REM) sleep, and non-REM sleep, according to the predominant EEG activity recorded on each sheet of the tracing (40 s), up to 540 sheets (6 h). The occurrence of slow wave and spindle activity was evaluated, both in basal condition and after drug administration, as parameters of cortical EEG synchronization, and scored as non-REM sleep. Evidence of theta wave in the occipital derivation, which indicates hippocampal EEG synchronization, associated with desynchronization of fronto-parietal derivations were scored as REM or wakefulness. The data were processed with an IBM-PC as described elsewhere (29). The duration in minutes of wakefulness, non-REM sleep, and REM were evaluated; latency of REM after the onset of non-REM sleep, number, and duration of REM episodes were then calculated. During the experiments of the conventional cycle, a trained observer recorded any significant changes in gross behavior of the animal on the EEG chart.

Experimental Design in the Dark Phase

Young male rats (75–100 g; Charles River, Calco, Italy) were maintained with the room in darkness from 9:00 a.m. to 9:00 p.m. for a 4-week adaptation period. After this period, the animals (weighing 250–350 g) underwent surgery and polygraphic recording as previously described. Throughout the studies the animals were maintained in a fixed environment at 22°C, with 50% humidity. EEG activity was recorded continuously for 6 h, from 9:00 a.m. to 3:00 p.m., concomitantly with the onset of the dark phase and vehicle or antiepileptic drugs were administered at 8:45 a.m.

Statistical Analysis

Sleep parameters after treatment were expressed as mean ± standard error (in min) and compared with the corresponding control value (vehicle). The effect of the different treatments was evaluated using Dunnett's *t*-test.

Drugs

Felbamate (Schering-Plough Research Institute, Kenilworth, NJ), lamotrigine (generously supplied by Wellcome Foundation, London, UK), carbamazepine (Sigma Chemical, St. Louis, MO), and phenobarbital (Pharmacia, Nerviano, Italy) were suspended in a 30% aqueous solution of polyethylene glycol 400; this vehicle alone was administered to control animals. Oral administration was chosen because the anticonvulsant activities of the four antiepileptic drugs examined were previously studied by other authors after PO administration in rats against the maximal electroshock and pentylentetrazol-induced seizures (27,38).

RESULTS

Light Phase

Control animals remained awake during the first recording hour, immediately after vehicle administration, and then spent a great amount of time sleeping (267 min of total sleep over 360 min; 74%). Felbamate (30, 100, and 300 mg/kg PO) did not modify gross behavior of the animals as compared with the control group. Likewise, no significant changes in behavior were observed following administration of either lamotrigine (3, 10, and 30 mg/kg, PO) or carbamazepine (10, 30, and 100 mg/kg, PO). Phenobarbital (30 and 100 mg/kg, PO) induced behavioral changes only at the high dose of 100 mg/kg. Specifically, the animals were sedated, fell into a prolonged state of stupor, locomotor activity was markedly decreased, and a progressive loss of reflexes was observed.

Felbamate did not affect either wakefulness or non-REM sleep (Table 1). Only at the high dose (300 mg/kg) did it reduce REM duration (45% decrease, $p < 0.05$). However, the number of REM episodes did not change significantly (Table 2).

TABLE 1

EFFECTS OF ANTICONVULSANT DRUGS IN THE SLEEP-WAKING CYCLE IN THE RAT DURING THE LIGHT PHASE

Treatment	Dose (mg/kg PO)	Wakefulness (min)	Non-REM Sleep (min)	REM Sleep (min)
Vehicle	–	93 ± 7	240 ± 6	27.3 ± 2.1
Felbamate	30	110 ± 12	223 ± 12	27.0 ± 4.2
	100	124 ± 21	214 ± 19	22.0 ± 5.4
	300	125 ± 21	219 ± 20	15.0 ± 2.3*
Carbamazepine	10	120 ± 16	217 ± 16	22.7 ± 1.8
	30	130 ± 11*	212 ± 10	18.5 ± 2.7
	100	105 ± 5	234 ± 5	21.7 ± 3.9
Lamotrigine	3	149 ± 13†	194 ± 13*	17.2 ± 3.6*
	10	151 ± 15†	193 ± 13†	16.3 ± 3.1*
	30	189 ± 15†	162 ± 13†	9.8 ± 2.6†
Phenobarbital	30	86 ± 12	250 ± 11	23.8 ± 3.2
	100	88 ± 13	264 ± 14	7.8 ± 1.7†

Data refer to 6 h of EEG recording. Each value is the mean ± SE for 6 rats, except the vehicle which is for 12 animals. Each rat was used once.

*$p < 0.05$, †$p < 0.01$ compared with the vehicle group (Dunnett's t-test).

Lamotrigine significantly increased wakefulness ($p < 0.01$) at each dose tested (Table 1). REM episodes decreased in both number and average duration, at 10 and 30 mg/kg, while REM latency increased at the high dose of 30 mg/kg (Table 2).

Carbamazepine, at 10 and 100 mg/kg, produced no effects on either wakefulness or non-REM sleep (Table 1). However, at 30 mg/kg, the drug increased wakefulness and affected REM by reducing number of episodes and increasing REM latency (Tables 1 and 2).

Phenobarbital, at 30 mg/kg, did not substantially influence either duration or onset of non-REM sleep (Table 1). At 100 mg/kg, the drug did not affect either wakefulness or non-REM sleep, but it significantly reduced REM duration (71% decrease; $p < 0.01$) over the 6 h experimental period. In addition, measures of REM sleep were significantly different from

TABLE 2

EFFECTS OF ANTICONVULSANT DRUGS ON REM SLEEP DURING THE LIGHT PHASE

Treatment	Dose (mg/kg PO)	REM Episodes		Latency to REM Onset
		Number	Mean Duration (min)	(min)
Vehicle	–	11.0 ± 0.6	2.5 ± 0.1	51 ± 10
Felbamate	30	11.7 ± 1.3	2.3 ± 0.3	48 ± 7
	100	8.8 ± 2.1	2.4 ± 0.1	96 ± 19
	300	7.0 ± 0.9	2.2 ± 0.2	99 ± 27
Carbamazepine	10	9.0 ± 0.7	2.5 ± 0.1	76 ± 14
	30	7.3 ± 1.3*	2.6 ± 0.1	138 ± 16†
	100	8.5 ± 1.1	2.5 ± 0.2	90 ± 15
Lamotrigine	3	8.0 ± 1.4	2.1 ± 0.1	67 ± 24
	10	6.7 ± 1.1*	2.5 ± 0.2	88 ± 16
	30	5.7 ± 1.4†	1.7 ± 0.1†	143 ± 29†
Phenobarbital	30	9.8 ± 0.9	2.4 ± 0.2	73 ± 15
	100	4.3 ± 1.1†	1.6 ± 0.3†	152 ± 32†

Data refer to 6 h of EEG recording. Each value is the mean ± SE for 6 rats except the vehicle which is from 12 animals. Each rat was used once.

*$p < 0.05$, †$p < 0.01$ compared with the vehicle group. (Dunnett's t-test).

those of controls: REM latency was markedly prolonged compared with control animals, and the number of episodes was significantly reduced ($p < 0.01$; Table 2).

Dark Phase

The sleep patterns displayed by control animals were completely different from those of animals kept under natural conditions (Table 3). During the 6 h recording time, animals already accustomed to the dark phase spent 54% in waking state, 40% in non-REM sleep, and 6% in REM stage (total sleep was 46%), while during the light phase rats spent more time asleep (69% for total sleep) than awake. The number of REM episodes was 9.3 ± 1.2 and its mean duration 2.1 ± 0.7 min, while the latency to the REM onset was 72 ± 18 min.

Under these conditions, felbamate (300 mg/kg PO) did not modify either duration or onset of non-REM sleep and wakefulness (Table 3). REM was affected by the drug, but only during the first 3 h of EEG recording (2.9 ± 0.8 vs. 8.0 ± 2.4 min, $p < 0.05$). However, the drug did not affect number of episodes, onset, and latency to REM.

Lamotrigine administered at 30 mg/kg PO showed a tendency to increase the amount of wakefulness and reduce non-REM sleep (Table 3). REM was significantly reduced over the 6 h period (60% decrease; $p < 0.01$). The effect on REM duration was associated with a reduced number of episodes (4.1 ± 0.8 vs. 9.3 ± 1.2, $p < 0.01$) and a tendency toward delayed latency (118 ± 27 vs. 72 ± 18 min, NS).

Carbamazepine (100 mg/kg, PO) did not change sleep-wake patterns (Table 3).

As expected, phenobarbital (100 mg/kg PO) increased the time spent in non-REM sleep by almost 55%, therefore reducing wakefulness (Table 3). These effects were also evident in the first 3 h segment of EEG recordings. The drug affected REM by reducing its duration by 71% in the first 3 h segment and by 59% over 6 h. It also reduced the number of episodes (4.4 ± 1.3 vs. 9.3 ± 1.2, $p < 0.05$).

As shown in Fig. 1, rats remained awake longer when the EEG recording was performed during the dark period and only phenobarbital, among the drugs examined, produced significant changes by increasing the amount of total sleep.

DISCUSSION

This study shows that the anticonvulsant drugs examined have different effects on the states of sleep-wakefulness in the rat. However, a limitation of the present studies is that drug effects were examined only following single dosing, whereas in the clinical setting CNS side effects of antiepileptic drugs are usually reported following chronic drug administration.

Felbamate was found to produce little or no effect on the behavioral states of sleep and waking under two different experimental conditions in the rat. It produced weak effects at a dose at least 5-fold those effective in protecting animals from convulsions, which are usually below 60 mg/kg (6,7). At the high dose of 300 mg/kg, felbamate reduced the amount of REM but induced no effect on either the total amount of sleep or duration of wakefulness. The data are consistent with clinical evidence that felbamate induces a low incidence of drowsiness in epileptic patients, particularly when the drug is taken alone rather than in polytherapy (4,17,35).

Lamotrigine affected various sleep parameters at all the doses examined. It is noteworthy that lamotrigine is able to block seizures induced by either maximal electroshock test or pentylentetrazol (27) at doses similar to those that influenced sleep in the present study. The most prominent effect was an increase of waking and reduction of total sleep, including REM. The effect was particularly evident during the light phase where, being asleep most of the time, the animals are more sensitive to stimulatory actions. This finding is somewhat unexpected because doses effective on sleep states in animals are similar to those used in human therapy (200–400 mg/day) (3,32) and, in addition, in one report on lamotrigine safety there does not appear to be a significant incidence of insomnia or other behavioral disturbances that could be related to sleep changes (2). However, more specific clinical data are needed to clarify the issue of possible CNS side effects associated with lamotrigine treatment. Moreover, in animals it would be useful to study whether lamotrigine effects on sleep states undergo tolerance when the drug is given over a chronic dose regimen.

Like felbamate, carbamazepine was found to have little or no effect on sleep states. Surprisingly, only at one dose point, 30 mg/kg, did the drug induce an increase in wakefulness and changes in REM sleep. In our experimental conditions it is difficult to explain the action of this dose of carbamazepine on wakefulness and REM sleep, and other approaches are necessary to clarify this effect. It is relevant to note that this dose was able to inhibit seizures induced by both maximal electroshock and pentylentetrazol (27,33). However, these effects were no longer evident at 100 mg/kg in either of the experimental conditions examined. The data are in line with clinical studies showing that carbamazepine has weak, if any, effects on sleep and causes little sedation at the therapeutic dose range (18,20).

TABLE 3

EFFECTS OF ANTICONVULSANT DRUG IN THE SLEEP-WAKING CYCLE IN THE RAT DURING THE DARK PHASE

Treatment	Dose (mg/kg PO)	Wakefulness (min)	Non-REM Sleep (min)	REM Sleep (min)
Vehicle	–	196 ± 9	144 ± 7	20.7 ± 3.3
Felbamate	300	202 ± 9	144 ± 10	14.1 ± 1.9
Carbamazepine	100	200 ± 13	143 ± 10	16.9 ± 2.8
Lamotrigine	30	216 ± 14	136 ± 13	8.3 ± 1.7†
Phenobarbital	100	110 ± 19†	242 ± 20†	8.4 ± 2.6†

Data refer to 6 h of EEG recording. Each value is the mean ± SE for 10 rats.

†$p < 0.01$ compared with the vehicle group (Dunnett's t-test).

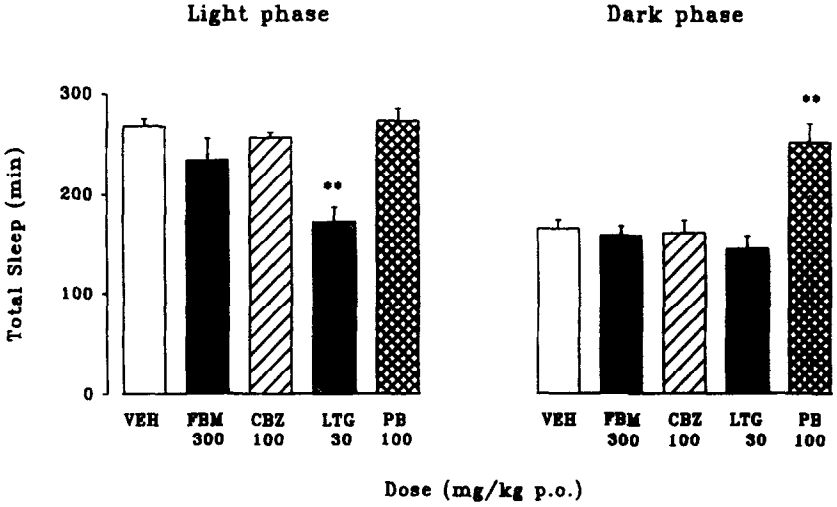

FIG. 1. Effects of antiepileptic drugs on duration of total sleep in rats. Total sleep was calculated as the cumulative amount of non-REM and REM over the 6 h recording time. Data represent the duration in min of total sleep (mean ± SE) obtained from groups of 6 animals (excepting vehicle, $n = 12$) for the light phase and 10 animals for the dark phase. VEH: vehicle; FBM: felbamate; CBZ: carbamazepine; LTG: lamotrigine; PB: phenobarbital. $^{**}p < 0.01$ compared with the respective vehicle group (Dunnett's t-test).

Of the drugs tested, only phenobarbital affected sleep states markedly. In the light phase, it reduced REM duration at 100 mg/kg and changed its distribution over the recording time. In the dark phase, phenobarbital increased sleep time and decreased REM duration through a reduction of both number of episodes and mean episode duration. Although the dose far exceeds the range used therapeutically and the changes induced in the sleep-wake cycle by the drug could be considered unspecific, it is significant that the effects observed are in agreement with the overt sleepiness or reduction of REM that is reported to occur when the drug is used in epileptic patients (14).

It is known that a variety of drugs can produce, especially at high doses, a reduction or even suppression of REM sleep (28). Most of these effects can be unspecific, however, because REM is a sleep stage sensitive to disturbances produced by a variety of stimuli. Indeed, REM may be specifically affected by drug administration (e.g., antidepressant drug treatment), but such effects are usually marked, dose-related, and manifested by a variety of changes involving onset of the first episode, number of episodes, and mean episode duration (23). Other drugs reducing REM, such as dopaminergic compounds, have primary stimulatory actions; that is, they increase arousal and consequently reduce the amount of total sleep, including REM (39). In view of this, the effect of felbamate or carbamazepine appears to be unspecific and more related to the perturbation that high doses can induce on rats' behavior.

The action of anticonvulsant drugs on the states of sleep and wakefulness has important implications in the therapy of epilepsy. Increased diurnal sleepiness as observed with phenobarbital, clearly impairs daytime functioning and more subtle changes may occur as a consequence of the continuous alterations of the REM sleep structure induced by drug treatment. It is known, for example, that some aftereffects of barbiturates may be caused by deprivation of REM after several nights of drug administration (22). Another aspect worth noting is the relationship between sleep and epilepsy. Many findings suggest that epileptic seizures may occur with different distribution across the states of sleep (31). For instance, non-REM sleep is apparently a permissive stage for the expression of some kinds of partial or generalized seizures. On the contrary, generalized discharges seldom occur during REM sleep. In addition to clinical evidence, a sleep phase relationship of EEG discharges and epileptic seizures has been demonstrated in animals (37). Thus, drug-related changes in sleep profile may affect the frequency and course of epileptic seizures. It is therefore important to characterize the effects of new antiepileptic drugs on sleep patterns.

GABA appears to be critical for the sedative action of some anticonvulsant drugs such as barbiturates or benzodiazepines (5,26). There are also studies suggesting that excitatory aminoacid system may influence the physiology of sleep. For example, direct brain administration of excitatory aminoacid agonists and antagonists alters sleep-related electrophysiology in rats (1). Furthermore, ketamine, a noncompetitive antagonist of the NMDA receptor-channel complex, with anticonvulsant properties, increases non-REM sleep duration in rats (9). In view of this, the differential effects of the four drugs examined on the sleep-waking cycle can be discussed on the basis of the mechanism of action that specifically characterizes each individual drug. Like other barbiturates, phenobarbital may activate $GABA_A$ receptors and then open chloride channels in the postsynaptic membrane, an action that causes electrical stabilization and inhibition of neuronal activity (34). It is known that GABA plays a role in the regulation of the sleep-wakefulness cycle, and in particular, stimulation of $GABA_A$ receptors increases the time spent sleeping (25). It has been suggested that felbamate interacts with neurotransmission mediated by excitatory aminoacids. In particular, this drug appears to interact primarily with the glycine site at the NMDA receptor complex, as shown by receptor binding studies (24), electrophysiological studies in rat hippocampal slices (8), and in vivo interaction studies in mice (6,7). This may explain

why felbamate has weak effects on the sleep-wake patterns, because antagonists at glycine site of the NMDA receptors appear to have little sedative or stimulating action (13). Increase of wakefulness induced by lamotrigine remains unexplained. The drug probably acts by inhibiting the release of glutamate (16) or blocking sodium channels (15), even though some studies indicate that the drug is not a NMDA antagonist. The mechanism by which lamotrigine affects sleep patterns still needs to be explored. As for carbamazepine, it is known that it acts at the ionic level and produces membrane stabilization by affecting sodium and potassium conductance (19). It seems therefore that these multiple actions of carbamazepine do not lead to significant changes of the mechanisms underlying the regulation of sleep-wake states.

In conclusion, the overall finding is that felbamate, of the new anticonvulsant drugs examined, does not produce EEG signs of sedation nor does it substantially alter the sleep structure at doses equal to and above those effective as anticonvulsant. Surprisingly, lamotrigine alters sleep stages and increases wakefulness even at low doses. In view of the importance of sleep phases in epilepsy and the potential CNS effects of antiepileptic drugs, the data can stimulate clinical studies focused on the assessment of specific drug actions on sleep patterns in patients. Further studies are necessary to understand the role, if any, of glycine/NMDA antagonists or, in general, of drugs that interact with excitatory neurotransmission in the physiology of sleep. The data can be of help to clarify the different profile of new drugs such as felbamate or lamotrigine on sleep-wake patterns.

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