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Sleep-wake mechanisms and drug discovery: sleep EEG as a tool for the development of CNS-acting drugs

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Sleep-wake alternation is an essential component of human biological rhythms, and physiological processes accompanying sleep are fundamental to body recovery. As reflected in waking performance, sleep is one of the major determinants of brain function. Quality of life, productivity, health, and effective education all depend on the quality of normal brain function. However, the economic and social development in our modern society has led, and will lead, to chronic disruption of sleep in a sizeable proportion of the population. The main contributors to these disruptions can be classified as either environmental (noise and light pollution), economic/societal (shift-work schedule), or pathological (sleep disorders). The detrimental effects of these factors on sleep increase with age and are expected to have an even larger impact in the future, given the aging population and the increased prevalence/incidence of shift work.

Sleep laboratory investigations constitute a unique noninvasive tool to analyze brain functioning. Polysomnographic recordings, even in the very early phase of development in humans, are mandatory in a developmental plan of a new sleep-acting compound. Sleep is also an interesting tool for the development of other drugs acting on the central nervous system (CNS). Indeed, changes in sleep electroencephalographic (EEG) characteristics are a very sensitive indication of the objective central effects of psychoactive drugs, and these changes are specific to the way the drug acts on the brain neurotransmitter systems. Moreover, new compounds can be compared with reference drugs in terms of the sleep EEG profile they induce. For instance, cognitive enhancers involving cholinergic mechanism have been consistently demonstrated to increase rapid eye movement (REM) sleep pressure, and studying drug-induced slow wave sleep (SWS) alteration is a particularly useful tool for the development of CNS compounds acting at the $5\text{-HT}_{2A/C}$ receptor, such as most atypical antipsychotics and some antidepressant drugs. The sleep EEG profile of antidepressants, and particularly their effects on REM sleep, are specific to their ability to enhance noradrenergic or serotonergic transmission. It is suggested that the effects of noradrenergic versus serotonergic reuptake inhibition could be disentangled using specific monoamine depletion tests and by studying drug effects on sleep microstructure. Dialogues Clin Neurosci. 2002;4:342-350.

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Selected abbreviations and acronyms

CNS	*central nervous system*
EEG	*electroencephalography*
GABA	*γ-aminobutyric acid*
GH	*growth hormone*
5-HT	*5-hydroxytryptamine (serotonin)*
NSRI	*noradrenaline and serotonin reuptake inhibitor*
PET	*positron emission tomography*
REM	*rapid eye movement*
SNRI	*selective noradrenaline reuptake inhibitor*
SSRI	*selective serotonin reuptake inhibitor*
SWS	*slow wave sleep*
TDT	*tryptophan depletion test*

At the present time, as much as one third of the adult population reports difficulty sleeping,[1-3] and sleep disturbance is considered as the second most common symptom of mental distress.[4] The widespread use of prescribed hypnotic medication as well as nonprescription remedies is an indirect reflection of the high frequency of sleep complaints.[2,5] Sleep disorders are often chronic conditions: one study found that over 40% of those reporting sleep problems had had them for more than 5 years.[1] Individuals reporting disturbed sleep are more likely to report emotional distress and recurrent health problems.[1] A major prospective investigation suggests that these problems are the consequence and not the cause of sleep difficulties.[6] Deviant sleep pattern has also been identified as a potentially important problem for physical health. Those who report shorter than average sleep duration ("short-sleepers") as well as those reporting long sleep duration ("long-sleepers") have been shown to have an increased risk of mortality.[7-9]

Despite recent inroads into understanding of the sleep-regulatory neural circuit,[10-13] current treatments for sleep disorders act via a limited number of pathways. Most hypnotics target GABAergic (GABA, γ-aminobutyric acid) activity globally in the brain. Other commonly used hypnotics that were not designed to treat insomnia (sedative antidepressants and antihistamines) have long half-lives and peripheral side effects. Current treatments for hypersomnia typically enhance dopaminergic transmission. New drugs designed for treating restless legs syndrome and periodic limb movement during sleep are needed. In a similar way, studies are needed to understand why most sedatives exacerbate disordered breathing during sleep, and to design countermeasures, or even drugs preventing, sleep apnea. As recently stressed by Mignot et al,[13] the rapid growth of basic and clinical sleep research promises to lead to new

and more targeted pharmacotherapy for sleep disorders. Thus, new drugs for therapeutic application in sleep disorder medicine are clearly needed. For this purpose, objective assessments of drug effects with polysomnographic recordings, even in the very early phase of development in humans, are mandatory in a developmental plan for a new sleep-acting compound. In the present paper, arguments for using sleep as a tool for the development of other drugs acting on the central nervous system (CNS) will be presented. In the following sections, we will discuss how the relationship between sleep physiology and neurotransmitter function could be used for the development of CNS-acting drugs.

REM sleep pressure as a surrogate marker of a cognitive enhancer acting on cholinergic neurotransmission

The cholinergic system is one of the most important modulatory neurotransmitters in the brain and controls many activities that depend on selective attention and conscious awareness. Drugs that antagonize muscarinic receptors induce hallucinations and reduce the level of consciousness, while the nicotinic receptor is implicated in the mode of action of general anesthetics.[14] In degenerative diseases of the brain, such as Alzheimer's disease, dementia with Lewy bodies, or Parkinson's disease, alterations in consciousness, loss of memory, visual hallucinations, or rapid eye movement (REM) sleep abnormalities have been associated with regional deficits in the cholinergic system. In the following sections, we will briefly discuss the value of using REM sleep as a surrogate marker of compounds acting on cholinergic neurotransmission, and particularly in the development of cognitive enhancers for Alzheimer's disease.

REM sleep

REM sleep was first described in 1953 by Aserinsky and Kleitman.[15] At regular 90- to 100-min intervals, they observed the spontaneous emergence of electroencephalographic (EEG) desynchronization accompanied by clusters of rapid saccadic eye movements. When subjects were awakened during such an episode, they generally reported that they had been dreaming. REM sleep is also called paradoxical sleep because of the close resemblance to the EEG of active wakefulness combined

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with a "paradoxical" active inhibition of major muscle groups that seems to reflect deep sleep. Normal sleep is characterized in EEG terms as recurrent cycles of non-REM and REM sleep of about 90 min. Non-REM sleep is subdivided into stages 1 through 4, with stage 1 being the lightest and stage 4 being the deepest sleep. In the successive cycles of the night, the amounts of stages 3 and 4 (also known as slow wave sleep [SWS]) decrease, and the proportion of the cycle occupied by REM sleep tends to increase, with REM episodes occurring late in the night having more eye movement bursts than REM episodes occurring early in the night.

Disturbances in REM sleep organization can be assessed by measuring its total amount (expressed in minutes or as a percentage of total sleep time), its onset latency (REM latency), its distribution across the successive non-REM/REM cycles during the night, and the actual number of rapid eye movements (REM activity) during this sleep stage or per minute of REM sleep (REM density). For instance, an increased propensity for REM sleep (or increased REM sleep pressure) is described as a greater amount of REM sleep mostly at the beginning of the night (also reflected by a shortened REM latency) and an increase in REM activity and REM density.

Acetylcholine, REM sleep, and Alzheimer's disease

At the present time, there is clear evidence for cholinergic mechanisms in the generation of REM sleep, and this has been the subject of many studies for the last four decades.[16-18] Animal studies have demonstrated that the expression of REM sleep-related physiology (eg, thalamocortical arousal, pontogeniculate-occipital waves, and atonia) depends upon a subpopulation of brain stem pediculopontine tegmental neurons that release acetylcholine to act upon muscarinic receptors.[19] Since a variable degree of cell loss in the pediculopontine region has been reported in Alzheimer's disease, it is tempting to speculate that the cholinergic deficit induces REM sleep–specific abnormalities such as decreased REM duration and density, increased REM latency, and REM sleep behavior disorder.[14,19]

More generally, human studies indicate that acute administration of muscarinic cholinergic agonists increase REM sleep propensity, whereas acute administration of muscarinic antagonists produce the opposite effect.[20] Based upon the pharmacological profile of the compounds used to manipulate sleep, it appears that both M_1

and M_2 muscarinic receptor subtypes are involved in REM sleep regulation.[20] Regarding acetylcholinesterase inhibitors, studies in healthy volunteers have shown that physostigmine,[21] tacrine,[22] and rivastigmine[23,24] increase REM sleep pressure. Interestingly, another acetylcholinesterase inhibitor, donepezil, may have a role in the treatment of REM sleep behavior disorder,[25] a syndrome characterized by the appearance of elaborate motor activity associated with dream mentation due to the intermittent loss of REM sleep muscular atonia.

In summary, the study of REM sleep propensity in normal subjects is a particularly useful tool in the development of CNS agents acting on cholinergic neurotransmission. This has been recently exemplified by studies using REM sleep changes as surrogate markers of the activity of acetylcholinesterase inhibitors. Drugs enhancing cholinergic transmission have been consistently demonstrated to increase REM sleep pressure. In this regard, cognitive enhancers involving a cholinergic mechanism have been shown to increase REM sleep amount, to shorten REM latency, and to increase REM activity and density. These characteristics are the sleep EEG "signature" of this class of drugs and could thus represent surrogate markers of activity.

Aging, SWS, and 5-HT$_2$ receptor antagonism

Role of SWS

It has long been assumed that sleep per se is essential for the restoration of body and mind; research conducted over the past three decades has led many experts to assume that SWS is centrally involved in such restorative process. In support of this assumption are numerous studies showing that SWS is totally recovered following sleep deprivation,[26] as well as several investigations linking SWS to growth hormone (GH) secretion,[27,28] which contributes to tissue repair. For instance, in monkeys, a positive correlation between the duration of SWS and the level of cerebral protein synthesis has been demonstrated.[29] Investigations of sleep-related changes in heart rate and blood pressure that found indices of parasympathetic dominance during non-REM sleep and particularly SWS,[30] and positron emission tomography (PET) scan studies showing that global cerebral glucose metabolism in humans is lowest in SWS,[31] are findings that further suggest a role of SWS in body restoration.

Further evidence for a role of SWS in human somatic restoration comes from studies showing that SWS increases following daytime exercise[32-34] and from the study of Kattler et al[35] showing that, in humans, slow wave activity increases during SWS in the central area contralateral to a prolonged vibratory hand stimulation experienced during the previous waking period. Regarding mental restorative processes, results of studies investigating the role of sleep in learning and memory suggest that memory formation is prompted by SWS-related processes with REM sleep promoting memory formation at a second stage (recently reviewed in references 10 and 36). In this regard, some studies suggested that cognitive performance (assessed through reaction time tasks) is related to amounts of SWS in healthy young volunteers[37] or to specific slow wave deficiencies in older insomniacs.[38]

Aging and SWS

Normal aging is characterized by the occurrence of several sleep disturbances.[39] Polysomnographic recordings identify an increase in the number and duration of awakenings during sleep and a lowering of SWS.[40,41] Nocturnal sleep is found to be less restorative, and aged subjects are prone to insomnia, daily somnolence, and napping.[42] Finally, since many aspects of cognitive performance decline with aging, it seems reasonable to question the relationship between SWS and cognitive performance among older adults.[43] It has been hypothesized that the amount of SWS could be directly related to the efficiency of neuronal connections in the cortex[44] and that aging leads to a decrease in the physiological process (process S) inducing SWS and favoring sleep continuity.[45,46]

5-HT$_2$ receptor and SWS

A body of evidence suggests that serotonergic transmission, particularly at the level of the 5-HT$_{2A/C}$ receptor, plays a major role in the induction of process S and SWS.[47] Drugs antagonizing the 5-HT$_{2A/C}$ receptor increase SWS, whereas 5-HT$_{2A/C}$ agonists have the opposite effect.[48] Spectral analysis of non-REM sleep shows a huge increase in slow wave activity with compounds blocking 5-HT$_{2A/C}$ transmission.[49,50] Although some antidepressant and antipsychotic drugs display this 5-HT$_{2A/C}$ antagonist profile and indeed have been shown to increase SWS,[51,52] up to now there is no drug marketed for sleep disorder that enhances SWS in a sustained manner. In contrast, chronic benzodiazepine administration has been shown to decrease SWS.[53] New nonbenzodiazepine hypnotics acting at the GABA$_A$ receptor, such as zopiclone, zolpidem, and zaleplon, have a more favorable profile in terms of sleep architecture, although none of them has demonstrated sustained SWS enrichment after repeated administration.[54]

In this regard, 5-HT$_{2A/C}$ receptor antagonists could thus be of great interest for alleviating age-related sleep disturbances and for ameliorating psychomotor and cognitive functions by restoring deep SWS, particularly in elderly insomniacs. There is preliminary evidence to suggest that repeated administration of ritanserin 5 mg (a 5-HT$_{2A/C}$ receptor antagonist) in middle-aged poor sleepers decreases the frequencies of awakening and improves subjective quality of sleep[55] and increases subjective alertness in narcoleptic patients[56] and in young healthy volunteers performing a driving test.[57] Furthermore, in young healthy subjects, Gronfier et al[58] found that the SWS enrichment induced by the acute administration of ritanserin 5 mg is positively correlated to the amount of GH secretion, suggesting a common 5-HT$_{2a/c}$–triggered stimulatory mechanism between GH secretion and delta wave activity.

The question of whether antagonizing the 5-HT$_{2A}$ or 5-HT$_{2C}$ receptor allows SWS enhancement is still unresolved. There are some data suggesting that 5-HT$_{2C}$ mediates SWS,[59,60] but Landolt et al[49] showed substantial SWS enhancement with SR 46349B, a specific 5-HT$_{2A}$ antagonist. Clozapine, which displays a weaker activity for 5-HT$_{2A}$ receptors, does not seem to affect SWS in schizophrenic patients or even tends to diminish it. Olanzapine induces clear-cut SWS enhancement in healthy subjects[61,62]; these effects seem to be mediated by 5-HT$_{2C}$ receptors, since allelic differences in the gene coding for this receptor influence SWS responses to olanzapine.[63]

In summary, compounds antagonizing 5-HT$_{2A/C}$ receptors could be valuable drugs for age-related sleep disturbances. In healthy subjects, studying drug-induced SWS alteration is a particularly useful tool for the development of CNS-acting compounds with 5-HT$_{2A/C}$-blocking properties.

REM sleep alterations as surrogate markers of antidepressant responsive conditions

Characteristic sleep EEG changes have been consistently identified in depressive illness. Lengthening of

sleep latency, frequent nocturnal awakening, and early morning wakening resulting in a decrease in total sleep time are the hallmarks of sleep continuity disturbances in major depression. With regard to sleep architecture, a deficit of SWS, especially during the first sleep cycle, has been consistently described. Disturbances in REM sleep organization consist of an earlier onset of this sleep stage, a greater amount of REM sleep at the beginning of the night, and an increase in the actual rapid eye movements (REM activity and REM density) during this sleep stage.[64,65] There is some evidence that these sleep abnormalities increase with the severity of the depression[66,67] and that they are more pronounced in older patients.[41,68] Furthermore, some studies, which controlled for the effects of these variables, indicate a comparable sleep EEG in different depressive subtypes, including the bipolar/unipolar distinction,[69] but suggest a role for endogenous and psychotic symptoms in the appearance of shortening of REM latency.[70,71]

Although the specificity of this sleep EEG profile to depression is not fully established, it should be noted that, according to Benca et al,[72] the most widespread and the most severe disturbances are found in patients with depressive disorder. Furthermore, REM sleep alterations have been reported in antidepressant-responsive conditions such as obsessive-compulsive disorder,[73] panic disorder,[74] depressed patients with anorexia nervosa[75] or alcoholism,[76] and, by some authors, in nondepressed patients with schizophrenia.[77] Thus, a body of evidence suggests that REM sleep disturbances could relate to antidepressant-responsive psychopathological states. It has been hypothesized that an imbalance between aminergic and cholinergic influences underlie REM sleep disinhibition (earlier onset, greater amount in the first part of the night, increase in the number of rapid eye movements) in depressive disorder.[78] Conversely, the ability of most antidepressant drugs to inhibit REM sleep might be attributed to facilitation of noradrenergic and/or serotonergic function or to muscarinic blockade.[52] In some cases, as with most tricyclic antidepressants, all three mechanisms may be involved. Antidepressant drugs without clear-cut REM suppressant effects (ie, amineptine, bupropion, nefazodone, tianeptine, trazodone, and trimipramine) have a common characteristic: their potency for inhibiting adrenergic or serotonergic uptake is either absent or moderate.[79,80]

Modeling a specific serotonergic and noradrenergic depressive profile by acute monoamine depletion

Serotonergic and catecholaminergic neurotransmission depletion paradigms have been shown to be useful research tools to evaluate the role of these neurotransmitter systems, both in the pathogenesis of depression and in the mechanisms of antidepressant treatment modalities.[81] It is postulated that sleep EEG disturbances in response to serotonergic and catecholaminergic challenges reflect pathologically diminished levels of serotonin or catecholamine release in depression, a condition that could briefly be elicited in healthy subjects with these depletion procedures. The only study to have tackled the question lends support to the idea that the tryptophan depletion test (TDT) in healthy subjects can mimic depressed patients in terms of neuroendocrine response to serotoninergic challenge; indeed, after performing a TDT in healthy subjects, Coccaro et al[82] showed an attenuated prolactin response to fenfluramine. Some studies[83-86] suggest that the TDT might be a valuable procedure to elicit typical sleep abnormalities of depression, and, in particular, an increased REM sleep pressure, a condition assumed to be associated with response to antidepressant drugs. It can be thus postulated that the TDT challenges using REM sleep pressure as a surrogate marker of depression might be useful models for studying the mechanisms of action of antidepressant drugs, since acute or chronic antidepressant drug administration should interfere with these sleep alterations. Indeed, in a recent study, we were able to demonstrate that the effects of the serotonin reuptake inhibitor fluvoxamine on REM sleep were partially inhibited by TDT challenge. Further developments of this technique will include a study with a specific noradrenergic reuptake inhibitor and the phenylalanine depletion challenge, and an attempt to replicate the sleep animal data suggesting that specific monoamine depletion could identify noradrenaline and serotonin reuptake inhibitors.[87]

Distinguishing the effects of SNRIs from those of SSRIs on the basis of sleep EEG recordings

Selective serotonin reuptake inhibitors (SSRIs), selective noradrenaline reuptake inhibitors (SNRIs), and dual noradrenaline and serotonin reuptake inhibitors (NSRIs) have all shown an REM-suppressant effect after single or repeated administration to healthy volunteers (for recent

reviews of the effects of antidepressants on sleep see references 52 and 88). There are also studies suggesting that these three types of antidepressant exhibit alerting effects (ie, tend to enhance vigilance and therefore induce arousal during sleep), although data are more sparse for SNRI and particularly NSRI. We suggest that sleep microarchitecture could distinguish SSRI from SNRI. Up to now, very few studies have investigated the effects of antidepressant drugs on the EEG spectral power values. For instance, the NSRI venlafaxine has been shown to decrease the power of delta and theta waves and increase fast beta-activities during non-REM sleep in depressed patients, suggesting that this compound could lighten sleep intensity.[89] Other studies[90,91] in depressed patients showed that citalopram decreased the non-REM EEG power in the 8 to 9 Hz range (lower alpha waves) and trazodone decreased the non-REM EEG power in the 13 to 14 Hz range (lower beta waves). One study in healthy subjects did not reveal any change in spectral power values in the delta, theta, alpha, beta, and gamma frequency ranges after 4 weeks of paroxetine administration.[92] There are some indications in the literature suggesting that serotonin and noradrenaline may play a different role in the regulation of sleep; indeed noradrenaline could be implicated in wake-promoting mechanisms and hyperarousal,[93,94] whereas serotonin could be more involved in sleep-promoting mechanisms.[95,96] For instance, animal studies suggest that noradrenaline and serotonin microinjections in the basal forebrain induce different modulation of gamma EEG activity and of the sleep-wake state.[97] It can thus speculated that sleep microstructure, reflecting these specific mechanisms, could be differently affected by the single administration of an SSRI, an SNRI, or an NSRI.

In summary, the sleep EEG profile of antidepressants and particularly the effects on REM sleep are specific to their ability to enhance noradrenergic or serotoninergic transmission. It is suggested that the respective effects of noradrenergic versus serotoninergic reuptake inhibition could be disentangled using specific monoamine depletion tests and by studying drug effects on sleep microstructure.

Conclusions

Sleep EEG recordings constitute a unique noninvasive tool to analyze brain functioning. The dynamic relationships between brain neurotransmitter systems can be directly addressed through the assessment of sleep physiology. Neurotransmission disturbances, such as those encountered in mental disorders, are reflected in spontaneous alteration of sleep continuity and architecture, or in aberrant sleep EEG responses to the administration of specific neuropsychopharmacological probes. Sleep laboratory investigations are particularly well suited to evaluating objective effects of psychoactive drugs on sleep and wakefulness. Moreover, new compounds can be compared with reference drugs in terms of the sleep EEG profile they induce. Finally, all-night sleep EEG spectral analysis provides a matchless technique to study the way drugs affect sleep microstructure, and therefore the core of sleep regulation mechanisms. ❏

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Los mecanismos del sueño-vigilia y el descubrimiento de fármacos: el EEG de sueño como una herramienta para el desarrollo de fármacos que actúan sobre el SNC

Las investigaciones de laboratorio de sueño constituyen una herramienta única, no invasora, para analizar el funcionamiento cerebral. Los registros polisomnográficos son mandatorios dentro del plan de desarrollo de un nuevo compuesto que actúe sobre el sueño, aun en la fase muy precoz del desarrollo en humanos. El sueño es también una herramienta interesante para el desarrollo de otros fármacos que actúen sobre el sistema nervioso central (SNC). Verdaderamente, los cambios en las características electroencefalográficas (EEG) del sueño representan una indicación muy sensible de los efectos centrales objetivos de fármacos psicoactivos. Estos cambios son específicos en relación a la forma de actuación del fármaco en los sistemas de neurotransmisión central. Sin embargo, los nuevos fármacos se pueden comparar con fármacos de referencia en términos del perfil EEG de sueño que ellos inducen. Por ejemplo, se ha demostrado consistentemente que los "aumentadores cognitivos" al incluir mecanismos colinérgicos incrementan la carga de sueño con movimientos oculares rápidos (MOR), y el estudio de la alteración en el sueño de ondas lentas inducida por fármacos es una herramienta particularmente útil para el desarrollo de compuestos para el SNC que actúan a nivel de receptores 5-HT$_{2A/C}$ como la mayoría de los antipsicóticos atípicos y algunos fármacos antidepresivos. El perfil EEG de sueño de los antidepresivos y, particularmente, los efectos sobre el sueño MOR son específicos en su capacidad para aumentar la transmisión noradrenérgica o serotoninérgica. Se ha sugerido que los efectos particulares de la inhibición de la recaptación noradrenérgica versus la inhibición de la recaptación serotoninérgica podrían ser aclarados utilizando pruebas específicas de depleción de monoaminas y mediante el estudio de los efectos de fármacos en la microestructura del sueño.

Mécanismes de veille-sommeil et découverte de médicaments : l'EEG de sommeil comme outil pour le développement de molécules agissant sur le SNC

L'exploration du sommeil en laboratoire constitue un outil non invasif remarquable d'analyse du fonctionnement cérébral. Les enregistrements polysomnographiques, même dans la phase très précoce du développement chez l'homme, sont impératifs dans le plan de développement d'une nouvelle molécule agissant sur le sommeil. L'exploration du sommeil est également un outil intéressant pour le développement d'autres médicaments agissant sur le système nerveux central (SNC). Les modifications des caractéristiques de l'électroencéphalogramme (EEG) au cours du sommeil sont en effet une indication très sensible des effets centraux objectifs des molécules psychoactives, et ces modifications sont spécifiques du mode d'action de la molécule sur les neurotransmetteurs cérébraux. De plus, les nouveaux traitements peuvent être comparés aux molécules de référence d'après le profil d'EEG de sommeil qu'ils induisent. Ainsi, les molécules améliorant la cognition par le biais du système cholinergique ont régulièrement démontré qu'elles augmentaient la propension aux mouvements oculaires rapides (MOR) durant le sommeil. L'étude des altérations du sommeil à ondes lentes induites par les médicaments est particulièrement utile pour le développement de molécules du SNC agissant au niveau du récepteur 5-HT$_{2A/C}$, tels la plupart des antipsychotiques atypiques et certains antidépresseurs. Le profil d'EEG de sommeil des antidépresseurs, et particulièrement les effets sur les MOR du sommeil, sont spécifiques de leur capacité à augmenter la transmission noradrénergique ou sérotoninergique. Il est suggéré que les effets respectifs de l'inhibition de la recapture noradrénergique et de l'inhibition de la recapture de la sérotonine pourraient être démêlés grâce à des tests spécifiques de déplétion des monoamines et en étudiant les effets des traitements sur la microstructure du sommeil.

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