Contribution of sleep research to the development of new antidepressants

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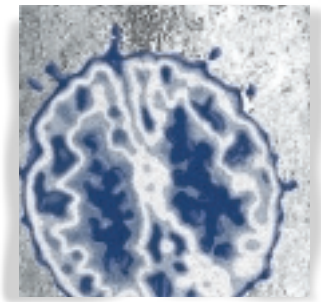

Several sleep anomalies are known to accompany depression and other psychiatric disorders, and to be partially modified by drugs efficient on clinical symptoms. Many puzzling theoretical questions remain, even after 30 years of research, because these drugs do not act in a uniform way: some reduce slow-wave sleep while others increase it; some prolong rapid-eye movement sleep latency, while others do not. The relationship between insomnia and depression is likely to be a close one, since a large majority of patients with depression suffer insomnia, and that insomnia can predate depression by a few years. However, questions remain here, too, since sleep deprivation is also an effective means to combat depression, and some patients present with hypersomnia rather than insomnia. This review details the action of all current classes of antidepressants on sleep. It examines the predictive value of baseline electronencephalographic sleep symptoms or early modifications due to treatment for eventual clinical efficiency. We will also discuss the two main theories on the relationship between sleep and depression. The action on sleep of all new drugs—and antidepressants in particular—is carefully examined during development, for insomnia is currently considered to be a major health concern in industrialized countries.

 Dialogues Clin Neurosci. 2005;7:305-313.

Keywords: *sleep research; drug development; antidepressant; treatment efficacy; EEG*

Since the discovery by Kupfer and Foster[1] of a link between depression and a shorter interval between sleep onset and the first episode of rapid eye movement sleep (REMS) than in controls, the relationship between psychiatric disorders and sleep has been the focus of intense research. Twenty years later, the results of a large meta-analysis[2] could be summarized as follows. The sleep of depressive patients is usually accompanied by several anomalies when compared with controls: (i) increased sleep onset latency; (ii) increased percentage of REMS; (iii) increased REMS density; (iv) decreased sleep maintenance; (v) decreased percentage of slow-wave sleep (SWS); and (vi) shortened REMS latency (RL). Although the relative influences of age, gender, and severity of the depressive episode on the observed sleep anomalies still need to be fully clarified, it is relatively easy to distinguish patients from controls on the basis of their sleep.

The above meta-analysis[2] also indicated that no sleep anomaly unambiguously distinguishes depression from other psychiatric symptoms, such as panic disorder,[3] generalized anxiety disorder,[4] obsessive-compulsive disorder,[5] schizophrenia,[6] severe dementia,[7] or borderline personality disorder.[8] Furthermore, no obvious distinction between depression subclasses (primary, endogenous, atypical, etc) has been demonstrated by elements of sleep polysomnography. Perhaps the best supported distinction is that between psychotic and nonpsychotic depression.[9] A few studies have tried the opposite route, ie, to cluster psychiatric disorders or subtypes as a function of biological markers,[10,11] but the results do not support qualitative distinctions and mutually exclusive subtypes. Instead, only quantitative differences emerged, favoring the concept of a "depressive spectrum."

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Selected abbreviations and acronyms

MAOI	*monoamine oxidase inhibitor*
MDD	*major depressive disorder*
NaSSA	*noradrenergic and specific serotonergic antidepressant*
REMS	*rapid eye movement sleep*
RL	*rapid eye movement sleep latency*
SNRI	*serotonin and norepinephrine reuptake inhibitor*
SSRI	*selective serotonin reuptake inhibitor*
SWS	*slow-wave sleep*
TCA	*tricyclic antidepressant*

As a consequence, sleep anomalies and manipulations are currently generally considered to be more useful for uncovering neurophysiological mechanisms underlying psychiatric disorders and symptoms and for understanding sleep itself than as a diagnostic tool for clinicians. Theories have been developed to explain what is observed in the sleep of untreated patients with major depressive disorder (MDD), the effects of drugs on their sleep, and the effects of sleep manipulations, such as total sleep deprivation or specific REMS deprivation.

Many interesting questions are still only partially resolved. Do effective antidepressants counteract what is observed in the sleep of untreated MDD patients? Does this mean that whatever is counteracted reflected depression in the first place? Is it through sleep modification that drugs act on depression, or are the observations merely epiphenomena? Are there clues that a given treatment will be effective in a fortnight? Are sleep anomalies signs of a biological trait? Do they represent the depressive state or do they go away after the clinical episode is gone? Do they represent scars of previous episodes? The situation for neuromediators is just as complex. Serotonin (5-hydroxytryptamine [5-HT]), for instance, is a target of choice in the fields of both depression and sleep disorders. Selective serotonergic agents are available, which could help us clarify the relationships between these two entities. However, the existence of several receptor sites ($5\text{-HT}_{1A\text{-}D}$, $5\text{-HT}_{2A\text{-}C}$, 5-HT_3, and 5-HT_4), which have agonist or antagonist interactions with each other, not to mention their potential interactions with γ-aminobutyric acid (GABA), noradrenaline (NA), or dopamine (DA) receptors, means that the map to be built is likely to be a complicated one.

Sleep research is also now an important part of the development of new psychotropic drugs, and almost every new agent has its effects on sleep carefully analyzed. As these data are the property of the patent owners and few are published in peer-reviewed journals, it is not always possible to precisely evaluate how sleep studies actually influence the future of these drugs, but it is likely to be substantial.

Insomnia is probably the main reason why action on sleep is studied so rigorously. Poor sleep has received an increasing amount of attention in the last decade.[12,13] More than 90% of depressive patients experience insomnia, whereas only 5% to 8% experience hypersomnia.[14] Persistent insomnia multiplies the risk of developing MDD within a year by three.[15] It increases the risk of recurrence of depression.[16] Mood disorders are frequent, but often go undiagnosed in chronic poor sleepers.[17] Optimal treatment of insomnia is thus currently a major health concern in industrialized countries. Since drugs can alleviate or worsen sleep initiation and maintenance, the development and selection of antidepressants in patients should take insomnia into account. Also, antidepressants may exacerbate restless legs or periodic limb movement syndromes, which results in a worsening of insomnia.

In this review, we will (i) describe the effects of the main antidepressants on sleep; (ii) examine which signs are predictive of good prognosis; and (iii) analyze the theoretical aspects of sleep anomalies in depression and actions on sleep by antidepressants.

Effects of antidepressant drugs on sleep

Monoamine oxidase inhibitors

Phenelzine, a monoamine oxidase inhibitor (MAOI), can almost completely suppress REMS after a few weeks of treatment,[18] both in healthy controls (HCs) and MDD patients. This is also the case with other MAOIs, such as nialamide, pargyline, and mebanazine. This suppression coincides with the beginning of the antidepressant effect, which suggests that a physiological link exists between REMS suppression and antidepressant effect. In most cases, the influence of MAOIs on SWS is not very pronounced, although they are usually considered to decrease sleep efficiency.[19]

Moclobemide, a reversible MAOI, has shown contradictory results, with one study showing it to be associated with better sleep efficiency and enhanced REMS with shorter RL in MDD patients,[20] and one study showing almost the opposite.[21]

Tricyclic antidepressants

The REMS-suppressing potencies of the tricyclic antidepressants (TCAs) are different from those of the MAOIs, as REMS can be suppressed almost immediately. Clomipramine, for instance, produces a profound suppression of REMS[22,23] in HCs. Imipramine[24] and desipramine[25] have also shown profound REMS-suppressing effects, at least in HCs and animals. The influence of TCAs on REMS appears to be less sustained than with MAOIs, as longitudinal studies show normal to increased levels of REMS.[26] Doxepin was also found to have REMS-suppressing effects.[22] Amitryptiline was found to reduce REMS in a group of depressed subjects.[27] A REMS rebound is usually observed on withdrawal.

Interestingly, not all TCAs have REMS-suppressing effects. For instance, trimipramine,[28] iprindole,[29] and viloxazine[30] have no significant effect on REMS.

As a group, TCAs tend to increase SWS, except for clomipramine.[31] One study on clomipramine in a group of MDD patients using spectral analysis has shown a significant increase in the delta bands, corresponding to SWS. Desipramine was associated with sleep-onset difficulty in a group of MDD patients.[32]

Tetracyclics

Mianserin has been shown to reduce REMS in rats.[33] It does not change REMS duration in HCs[34] and MDD patients.[35] Maprotiline reduces REMS and increases stage 2 sleep in HCs.[36] These compounds tend to increase SWS.[33]

Selective serotonin reuptake inhibitors

The selective serotonin reuptake inhibitor (SSRI) fluvoxamine was found to suppress REMS and prolong the RL in a group of MDD patients, but had no significant action on SWS or delta band in spectral analysis.[32] Paroxetine was shown to reduce total sleep time and sleep efficiency in MDD patients,[37,38] while REMS decreased and RL increased.

In MDD patients, fluoxetine was associated with more awakenings, decreased sleep efficiency, decreased SWS, and decreased sleep efficiency. RL is prolonged and REMS is reduced.[39-41] Treatment of MDD patients showed sertraline to prolong sleep latency and decrease REMS time.[42]

Citalopram was shown to suppress REMS in a sustained manner and to be accompanied by REMS rebound at withdrawal.[43] No change was observed in the delta band upon spectral analysis.

Trazodone (100 to 150 mg/day) was found to reduce REMS and increase SWS, as well as subjective estimations of sleep quality in a group of middle-aged patients with insomnia.[44] Mouret et al[45] found total sleep time and SWS to be increased with 400 to 600 mg/day of trazodone in a group of MDD patients, whereas REMS and RL were not significantly modified. In another study using lower doses, Van Bemmel et al[46] found no changes in SWS.

Nefazodone was shown to reduce the number of awakenings and improve sleep efficiency, and also stabilize,[40] or even increase,[47] REMS time in HCs and MDD patients. SWS was reduced. SSRIs have been shown to exacerbate periodic limb movement syndrome.[48]

Serotonin and norepinephrine reuptake inhibitors

The serotonin and norepinephrine reuptake inhibitor (SNRI) venlafaxine was found to increase wake time and sleep stages 1, 2, and 3 in HCs. REMS was strongly suppressed and RL was prolonged.[47,49]

Noradrenergic and specific serotonergic antidepressant

The noradrenergic and specific serotonergic antidepressant (NaSSA) mirtazapine was shown to promote sleep in HCs. It shortened sleep onset and deep sleep was increased. RL was increased; nighttime wakening was reduced.[50] In MDD patients, sleep efficiency and total sleep time were increased. REMS was not affected.[51]

Other antidepressants

Tianeptine was not shown to suppress REMS in a significant way in HCs[52,53] or patients with comorbid depression and alcoholism.[54] Moreover, a study in young HCs found no effect on EEG sleep parameters at therapeutic dosages (37.5 mg/day).[55] The same study found improvement in sleep with tianeptine using the subjective Leeds sleep evaluation questionnaire.

Summary of effects of common antidepressants on sleep

Table I summarizes the main results cited above. The large majority of antidepressant drugs suppress or elim-

inate REMS almost immediately (TCAs, SSRIs, SNRIs, and NaSSAs) or after about 2 weeks of treatment (MAOIs). There are, however, a few notable exceptions (trimipramine, iprindole, tianeptine, viloxazine, nefazodone). Deep sleep can be either increased (trazodone, nefazodone, mirtazapine), not modified (most MAOIs, fluvoxamine), or decreased (clomipramine, desipramine, phenelzine, fluoxetine, paroxetine, sertraline, venlafaxine). The effects after long-term treatment are not well documented, but tend to show a reduction of the initial impact. There are few differences as a whole between the effects of pharmacological substances on HCs and patients. Spectral analysis in the delta band has generally confirmed what is observed for visually analyzed deep sleep. As we can see, antidepressants generally do have effects on sleep, although these vary in direction and intensity from drug to drug. These actions are due to the neuromediators targeted to combat depression, and which also act on sleep. The various receptor profiles on which they exert their action explain these differences.

Prediction of treatment efficacy

Polysomnographic measurements for predicting future efficacy

Because a delay of at least 2 weeks exists between the first intake of an antidepressant drug and its clinical action in relieving symptoms, the matching of the right antidepressant to a given patient can be quite a challenge. Drug dosage modifications do not yield immediate results either, and switches between compounds include periods of overlap, which may prove uncomfortable for the patient. In this context, any markers predicting the efficacy of a substance from baseline characteristics or very soon after treatment initiation (pharmacological, psychotherapeutic, or sleep changes) could make optimal treatment selection a faster and smoother process. Several predictors of future efficiency have been evidenced.

- Pretreatment (baseline) short RL has been linked to positive response.[56]
- Pretreatment all-night electroencephalographic (EEG) spectral analysis has also been shown to predict clinical response. Higher delta band and lower alpha, beta, and theta band power were found in future responders.[57] This, however, was not confirmed in another study in MDD patients.[58]
- Pretreatment higher levels of REMS density predicted poor prognosis.

Initial REMS suppression by the substance has been tested for its prognostic value. Kupfer et al[59,60] and Gillin et al[61] have shown that REMS suppression in the initial two nights of TCA treatment was predictive of therapeutic efficacy. Höchli et al[62] have shown similar results for clomipramine. This finding has not been confirmed with SSRIs. Although promising, these strategies are actually seldom used in practice.

Specific antidepressants for specific depression subtypes?

Just as the search for sleep correlates of the different subtypes of depression has generally been elusive, the demonstration that it is more efficient to target specific neuroreceptors as a function of the clinical characteristics of a patient (ie, more serotonergic, more noradrenergic, and more dopaminergic treatments) has not been very conclusive so far. This is likely to be due to the complexity and uncovered interactions between neuromediators and receptors.[32]

Theories

Several arguments support the hypothesis that sleep dysregulation is closely linked to the underlying pathophysiology of depressive disorders: (i) patients suffer from either insomnia or hypersomnia in almost all cases; (ii) patients with chronic insomnia alone are at risk for developing depression or suffering a recurrence of depression; (iii) pharmacological agents active on depression modify sleep, usually counteracting what is observed in these patients at baseline; and (iv) sleep deprivation is an efficient way to relieve depression symptoms in 50% of the patients, although this effect is only transient. Two main theories have attempted to explain what is observed.

S-deficiency

If depression is characterized by insomnia, does the restoration of sleep continuity and intensity parallel or predict clinical recovery? One of the hypotheses of depression is that the first step lies in a weakening of SWS or spectral delta band power, which in turn allows for REMS to use the lost ground and appear sooner in

	HCs/MDD	REMS (acute)	RL (acute)	SWS (acute)	Effect (acute)	REMS (>21 days)	RL (>21 days)	SWS (>21 days)	Effect (>21 days)	REMS (rebound on withdrawal)
• MAOIs										
Phenelzine	HC			-	NS					
	MDD	NS	NS		NS	--	+++			+
Moclobemide	HC	-	NS	NS	-					
	MDD	(-)	+		NS	NS	+		NS	+
• TCAs										
Clomipramine	HC	--	++	-	-	--			-	+
	MDD	--	+++	-	-	-	++		-	
Amitriptyline	HC	-	++	+	+	--	+		NS	+
	MDD	-	++	++	NS	-	++		+	+
Trimipramine	HC	NS	+	NS	+		+			NS
	MDD	NS	+		+	NS	NS		+	
Mianserin	HC	-	+	+	+					
	MDD	(-)	+	NS	+	-	+		+	
Trazodone	HC	-	+	+	NS					+
	MDD	NS	NS		+	NS	NS		+	
Nefazodone	HC	+	NS	NS	NS	+	NS	NS		
	MDD	NS	-	-	+	NS	-		+	
• SSRIs										
Fluoxetine	HC	-	+	-	-	-	++		-	+
	MDD	NS	NS	-	NS	(-)	+		-	NS
Citalopram	HC	--	++	NS	-	-	++		-	+
	MDD	--	++		-	-	+		NS	+
Fluvoxamine	HC	--	++	NS	-	-	++		-	+
	MDD	--	++	-	-	-	+		NS	+
Sertraline	HC	--	++	NS	-	-	++		-	+
	MDD	--	++		-	-	+		NS	+
Paroxetine	HC	--	++	NS	-	-	++		-	+
	MDD	--	++	-	-	-	+	-	NS	+
• NARIs										
Reboxetine	HC									
	MDD	NS	NS		-	-	+		-	
• SNRIs										
Venlafaxine	HC	--	++		-					
	MDD									
• NaSSAs										
Mirtazapine	HC	NS	+	+	+					
	MDD	NS	NS		+	NS	+		+	
• Other antidepressants										
Tianeptine	HC	+	-	+	NS	NS				+
	MDD	+	-	NS						+

Table I. Main effects of antidepressants on sleep. NS, not significant; HC, healthy control; MDD, major depressive disorder; REMS, rapid eye movement sleep; RL, REMS latency; SWS, slow-wave sleep; (+), slightly positive effect; +, positive effect; ++, marked positive effect; (-), slightly negative effect; -, negative effect; --, marked negative effect; MAOI, monoamine oxidase inhibitor; SSRI, selective serotonin reuptake inhibitor; NARI, noradrenaline reuptake inhibitor; SNRI, serotonin and norepinephrine reuptake inhibitor; NaSSA, noradrenergic and specific serotonin reuptake antidepressant.

the night, with increased REMS and shorter REMS latency.[63] This hypothesis is itself derived from Borbély's general model of sleep regulation,[64] where process "S" represents EEG sleep delta bands corresponding to deep sleep (roughly corresponding to stages 3 and 4 on visually analyzed hypnograms). One of the ways to test this hypothesis was to measure the sleep EEG spectral power response to antidepressants. A study using spectral analysis and comparison of the effects of trazodone and citalopram in a group of MDD patients was performed to measure whether a parallel could be drawn between potential modifications and timing of clinical recovery. The study found that the delta band did not show significant modifications during the 5 weeks of treatment and the timing for changes in other bands did not correlate with clinical changes.[65] Furthermore, antidepressants vary considerably in their actions on sleep continuity, from deterioration to improvement, so that the role of non-REMS restoration remains elusive.

Excessive REMS pressure

Vogel et al[66] have reviewed 251 studies focusing on the influence of a variety of drugs (barbiturates, benzodiazepines, antidepressants, antipsychotics, lithium, opioids, amine precursors, and ethanol) on REMS in animals, human HCs, and patients with MDD. Their conclusion was that all drugs that produce large and sustained decrements of REMS time and were followed by a REMS rebound upon withdrawal are active on endogenous depression. Treatment by antidepressant drugs—and also by (partial, REMS-specific; or full) sleep deprivation, electronconvulsive treatment, or psychotherapy—would parallel or act through the reversal of the abnormal characteristics observed in the sleep of depressed patients. Whatever the underlying mechanism, RL is shortened during depression and should be prolonged; REMS percentage is higher during depression and should be reduced.

It appears, however, that the general rule of REMS-reducing, RL-lengthening efficient antidepressants suffers many exceptions, because several efficient drugs do not reduce REMS *(Table I)*. Therefore, either more than one mechanism is at work and only a fraction of the antidepressants comply with the rule, or sleep modifications during treatment are only indirectly linked to efficiency against depression. Furthermore, the degree to which REMS is suppressed and the time where the suppression occurs do not in general correspond to clinical improvement (except for MAOIs).

Summary of theories

Although sleep and the neurophysiological mechanisms that determine it are likely to be very close to the mechanisms that define depression, they are most probably not identical and we certainly cannot claim that sleep ought to be corrected (REMS reduced, RL prolonged, SWS/delta sleep increased, better continuity) in order for depression to be relieved. Sleep is not a mere epiphenomenon, as testified by the frequent association with insomnia, the efficiency of sleep manipulations on depression, and the modifications induced by antidepressant drugs, but it is probably not a necessary component of the mechanisms of depression.

Conclusions

More than 30 years of sleep research in the domain of depression and other psychiatric disorders have yielded many interesting results. On the other hand, several dead-end alleys have been explored, following promising concepts and generating some frustration. We are still missing a global and comprehensive theory to explain what is observed, both at baseline and after some time of treatment. This should be considered in the context of the huge complexity of the issues. To start with, the functions of sleep itself are still very poorly understood (see reference 67 for a recent overview on the issue), so that we hardly can tell how much sleep or what kind of sleep is recommended for a given person. The distinction between REMS and non-REMS implies another level of complexity that is not yet resolved. Depression is currently regarded as part of a spectrum of disorders, ranging from anxiety to psychosis. Neuromediators are numerous and can be both agonists or antagonists of each other, which results in major difficulties in determining what does what. It is therefore no surprise that no simple and easy answer to these complex issues is yet at hand. More insight and more research are definitely needed.

One domain where sleep research is already useful today is insomnia, for it may predate, accompany, or worsen depression. The finding of new antidepressant drugs that will also take good care of insomnia without prompting daytime sleepiness will undoubtedly increase compliance and prognosis. ❑

Contribución de la investigación del sueño al desarrollo de nuevos antidepresivos

Se sabe que algunas anomalías del sueño acompañan a la depresión y a otros trastornos psiquiátricos, y pueden ser parcialmente modificadas por fármacos eficaces sobre síntomas clínicos. A pesar de 30 años de investigación, aun muchas preguntas teóricas siguen constituyendo un enigma ya que estos fármacos no actúan de una manera uniforme: algunos reducen el sueño de ondas lentas mientras que otros lo aumentan; algunos prolongan la latencia del sueño de movimientos oculares rápidos y otros no. La relación entre insomnio y depresión es probable que sea estrecha ya que la mayor parte de los pacientes con depresión padece insomnio, y el insomnio puede anteceder a la depresión en algunos años. Sin embargo, hay otras preguntas que persisten ya que la privación de sueño constituye un recurso eficaz para combatir la depresión y algunos pacientes presentan hipersomnia más que insomnio. Esta revisión detalla la acción de todos los antidepresivos actuales sobre el sueño. Se examina el valor predictor de síntomas del electroencefalograma de sueño basal o modificaciones precoces debidas al tratamiento para determinar la eventual eficacia clínica del fármaco. También se discuten las dos principales teorías acerca de la relación entre sueño y depresión. Los efectos sobre el sueño de todos los nuevos fármacos y en particular de los antidepresivos son examinados cuidadosamente durante el proceso de desarrollo de éstos ya que se considera que el insomnio actualmente constituye un gran problema de salud en los países industrializados.

Contribution de la recherche sur le sommeil au développement de nouveaux antidépresseurs

De nombreuses anomalies du sommeil accompagnent la dépression ainsi que d'autres troubles psychiatriques et sont partiellement modifiées par les substances efficaces sur les symptômes cliniques. Plusieurs questions théoriques troublantes persistent après 30 années de recherche, puisque ces substances n'agissent pas de façon uniforme : certaines réduisent le sommeil profond à ondes lentes alors que d'autres l'accroissent ; certaines prolongent la latence d'apparition du sommeil paradoxal alors que d'autres, non. Les liens entre insomnie et dépression sont vraisemblablement étroits puisqu'une grande majorité des patients présentant une dépression sont insomniaques et que l'insomnie anticipe parfois la dépression de plusieurs années. Des questions restent posées ici aussi, puisque la privation de sommeil est aussi un traitement efficace de la dépression, et que certains patients sont hypersomniaques au lieu de dormir trop peu. La revue présentée ici détaille l'action de toutes les classes connues d'antidépresseurs sur le sommeil et examine la valeur prédictive sur l'efficacité clinique à venir de symptômes EEG (électroencéphalogramme) de départ ou de modifications précoces par le traitement ; les deux théories principales touchant aux relations entre sommeil et dépression sont débattues. L'action sur le sommeil de nouvelles substances, et des antidépresseurs en particulier, est examinée en détail pendant leur développement, du fait que l'insomnie est considérée actuellement comme un problème de santé majeur dans les pays industrialisés.

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