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Time has always been in the focus of attention of psychiatrists, with authors like Minkowski and Strauss interpreting psychopathological changes in time perception as the “slowing down or inhibition of lived time in depression.”¹,² This perceived slowing down of time is very characteristic of depression and is accompanied by hopelessness in regard to the future, while clinging to the past. In contrast, manic patients experience time as being sped up and focus primarily on the present, and tend to neglect the past and future, as described recently by Ghaemi.³

When diagnosing mental disorders, clinicians elicit information about symptoms, identify one or several syndromes, and based on these, finally come to a diagnosis. Although this approach appears very cross-sectional, as if one were “freezing” the patient’s condition in time, the dynamic dimension of time is essential in the process. This dimension is taken into account, for example, by the Diagnostic and Statistical Manual of Mental Disorders (DSM)–IV requirement of at least 2 weeks’ symptom duration for a diagnosis of depression, or by the observation of seasonal changes in symptom severity.

As this issue of Medicographia makes abundantly clear, the concept of time plays multiple and ubiquitous roles in depression.

Time and depression both are complex concepts. In physics, time, along with space, length, mass, etc, belongs to the rarified group of fundamental quantities, for which the only definition can be a circular one: ie, time can only be defined by time, length by length, etc. Time does not derive from anything else than time, but leads to a host of quantities that derive from time, such as velocity, acceleration, frequency, etc, so that time can be used to define velocity, but the reciprocal isn’t true.

If we now look at time in depression, we find that in some cases, time can be used to define depression, in others not.

It is increasingly clear that the normal function of time is “lost” in depression, hence the cover title of this issue of Medicographia: “In search of lost time: À la recherche du temps perdu” taken from Marcel Proust’s monumental work. The most obvious alteration concerns the subjective perception of time, which in most patients suffering from depression is perceived as passing more slowly. But this perception is very difficult to differentiate from the normal subjective perception of time, which varies widely depending on the social context, attention and vigilance, and mood.

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Time in depression

by J. Mendlewicz, Belgium
Therefore, this subjective manifestation reported by depressed patients of time passing more slowly although it derives from depression (as velocity derives from time) cannot be used to define depression (just as velocity cannot be used to define time).

But other time-related symptoms of depression have totally different implications. Depression leads to disturbances in physiological rhythms, which result in disturbances in circadian sleep-wake cycles, hormonal secretion patterns, and fluctuations in mood, all of which can be objectively measured. In this case, these disturbances, which are associated with depression, can, contrary to our first example (perceived slow passing of time), be used to define depression.

These disturbances can also be used to define a novel therapeutic approach, which by resetting the internal biological clock restores circadian rhythms, thereby leading to clinically demonstrable efficacy on depression symptoms. This is what agomelatine—released in 2009 in Europe for the treatment of depression—does, through its action on the melatonergic MT1 and MT2 receptors, and the 5-HT2C receptors.

Beyond these “transversal” time-related symptoms, there are the “longitudinal” time-related symptoms, since depression evolves over a long period of time, with a profound impact on a person’s life, and is often associated with long-term psychosocial consequences. Taking this idea one step further, if we symbolize the whole of a person’s life by a line, there are sections along this timeline at which a person is more prone to the risk of developing depression than others, some common to all, like higher age, others depending on each individual’s lifetime events: psychological trauma, a succession of traumas, shortly before or after giving birth, following the onset of menopause, or in the wake of somatic diseases such as diabetes or cancer.

Time also plays a role before depression has been formally identified as such. In spite of the availability of adequate health care systems in many parts of the world, the time between the occurrence of the first depressive symptoms and diagnosis is often considerable. Time also is an issue after diagnosis, when the patient is under treatment, because the time-to-onset of improvement in symptoms is dependent on a latency period that is usually of 4 to 6 weeks before improvement is reported, and this in spite of the fact that pharmacological and psychosocial treatments are constantly improving, and display increasing efficacy and safety. Nowadays, fast onset of action has become a key performance indicator for antidepressants—both in terms of patient expectations, as well as being a goal of research to develop new agents with more rapid onset of action. This also has obvious major health economics implications: the STAR*D trial (Sequenced Treatment Alternatives to Relieve Depression) showed that early symptomatic relief is a positive predictor of remission. Improving the efficacy of treatment will consequently alleviate the burden of depression over time, both for the individual and for society.

In addition to the “two-dimensional relationship” between time and depression, as described above, some authors, like de Leval, have attempted to develop a “three-dimensional approach” involving time, depression, and quality of life. In his model, de Leval describes the dislocated temporal horizon of the depressed patient, who experiences time as passing more slowly, the present as being dissociated from the past, and who no longer recognizes the potential of the future, but views it with hopelessness. For depressed patients, the past increasingly becomes a “golden age” when life was better than now. These patients would like to go back to their past in a quest that becomes their only future. De Leval postulates a “phenomenological depression” related to the perception of a gap between a healthy past and the present illness. “The greater the gap between past and present, the greater the phenomenological-depression.” In de Leval’s theory, quality of life is perceived as the gap between actual experience and future aspirations and is defined as being “the appropriateness of future aspirations to the present” or “the making present of the future.”

The impact of depression on quality of life becomes even clearer when one tries to quantify quality of life. Years Lost to Disability (YLD) is a measure of the equivalent years of healthy life lost through time spent in states of less than full health, and thus statistically quantifies decreased quality of life through the amount of time lost. When all the years of life with reduced capability are added up for all sufferers of an individual condition and weighted according to the condition’s particular “disability weight,” a total of YLD is obtained for the condition.

In this issue of Medicographia, several renowned authors elucidate these concepts and aspects of time as a relevant entity in depression, approaching them from several angles:

• The temporal characteristics of depression from the epidemiological perspective are the topic of the contribution by H. U. Wittchen and S. Uhmann, who describe aspects and risk factors of depression pathogenesis.
• G. M. Goodwin discusses time in the course of depression, aspects of the prediction of further episodes, and the timing and duration of treatment.
• P. Gorwood looks at subjective time and the perception of time by depressed patients, and the therapeutic implications.
• H. J. Möller, F. H. Seemüller, and M. Riedel reflect on objective aspects of time and their importance in depression, and the predicament of antidepressants with a slow onset of action when it is known that early improvement is a predictor of response and remission.
• G. Hajak and M. Landgrebe enlarge on the linear concept...
of time by exploring circadian rhythms and their role in depression, which extends beyond diurnal mood variation in depressed patients.

◆ The bridge from time to clocks will be spanned by D. Tardito, G. Racagni, and M. Popoli, who present the pharmacology of the internal clock and the regulation of circadian rhythms at the intercellular and intracellular levels.

◆ C. Muñoz describes the efficacy of Thymanax, the first melatonergic antidepressant, at each and every time phase of the management of depression, based on the resynchronization of circadian rhythms.

◆ In the Controversial Question, a panel of experts discuss time in relation to the speed of onset of antidepressant efficacy.

◆ P. Lemoine addresses the issue of social rhythms in depression in an interview, by showing how to measure them, how their resynchronization can provide alleviation of symptoms, and how this can be achieved.

◆ S. H. Kennedy, P. Giacobbe, and S. Rizvi describe the criteria for measuring early onset of efficacy in the treatment of depression.

◆ Finally, B. Saletu, P. Anderer, and G. M. Saletu-Zyhlarz show how advanced imaging technology allows us to visualize and thus better understand the effects of antidepressants in the brain.

References

Keywords: time; concept; depression; onset; circadian rhythm; body clock
Le temps dans la dépression

par J. Mendlewicz, BELGIQUE

Le temps a toujours fait l’objet d’une attention particulière de la part des psychiatres, avec des auteurs comme Minkowski et Strauss interprétant les changements psychopathologiques de la perception du temps comme le « ralentissement ou l’inhibition du temps vécu dans la dépression »1,2. Ce ralentissement perçu du temps est très caractéristique de la dépression, et s’accompagne d’une vision sans espoir de l’avenir, parallèlement à un cramponnement au passé. À l’opposé, les patients maniaques ressentent une accélération du temps, se concentrent principalement sur le présent, et ont tendance à négliger le passé et l’avenir, comme l’a récemment décrit Ghaemi3.

Dans l’exploration de troubles mentaux, les cliniciens obtiennent des informations au sujet des symptômes, identifient un ou plusieurs syndromes, et sur la base de ces observations finissent par poser un diagnostic. Toutefois, cette approche semble très transversale, comme si l’état du patient était « gelé » dans le temps, alors que la dimension chronologique dynamique est essentielle dans le processus. Cette dimension est prise en compte, par exemple, par le Manuel Diagnostique et Statistique des Troubles Mentaux (Diagnostic and Statistical Manual of Mental Disorders [DSM]–IV), qui exige une durée d’au moins deux semaines pour un diagnostic de dépression, ou par la constatation de changements saisonniers dans la sévérité des symptômes.

Comme ce numéro de Medicographia le montre de façon particulièrement claire, le concept de temps joue des rôles multiples et omniprésents dans la dépression.

Le temps et la dépression sont tous deux des concepts complexes. En physique, le temps, avec l’espace, les dimensions, la masse, etc., appartiennent au groupe très « sélect » des quantités fondamentales, pour lesquelles la seule définition ne peut être que circulaire : c’est-à-dire, que le temps ne peut être défini que par le temps, une dimension par une dimension, etc. Le temps ne provient de rien d’autre que du temps, mais conduit à une grande variété de quantités qui en dérivent, par exemple, la vitesse, l’accélération, la fréquence, etc. Ainsi, le temps peut être utilisé pour définir la vitesse, mais la réciproque n’est pas vraie.

Si nous examinons la notion de temps dans la dépression, nous constatons que le temps peut être utilisé pour définir la dépression dans certains cas, mais pas dans tous. Il devient de plus en plus clair que la fonction normale du temps est « perdue » dans la dépression, d’où le titre de couverture de ce numéro de Medicographia : « À la recherche du temps perdu », emprunté au chef-d’œuvre de Marcel
Proust. L’altération la plus évidente concerne la perception subjective du temps, qui, chez la plupart des patients souffrant de dépression, est ressentie comme s’écoulant plus lentement. Toutefois, il s’agit d’une perception qu’il très est difficile de différencier de la perception subjective normale du temps, et qui varie largement en fonction du contexte social, de l’attention et de la vigilance, et de l’humeur. Par conséquent, la manifestation subjective d’un écoulement plus lent du temps observée chez les patients dépressifs si elle dérive de la dépression (comme la vitesse dérègne du temps) ne peut pas être utilisée pour définir la dépression (comme la vitesse ne peut pas être utilisée pour définir le temps).

Néanmoins, d’autres symptômes de la dépression liés au temps ont des conséquences totalement différentes. La dépression conduit à des troubles des rythmes physiologiques, qui provoquent des perturbations des cycles circadiens de sommeil et de veille et des profits de sécrétion hormonale ainsi que des fluctuations de l’humeur, autant de manifestations pouvant être objectivement mesurées. Dans ce cas, ces altérations, qui sont associées à la dépression, peuvent, contrairement à notre premier exemple (perception d’un écoulement ralenti du temps), être utilisées pour définir la dépression.

Au-delà de ces symptômes « transversaux » liés au temps, il existe des symptômes « longitudinaux » liés au temps, dans la mesure où la dépression évolue sur une période prolongée, qui exercent un impact profond sur la vie de la personne, s’accompagnant souvent de conséquences psychologiques à long terme. En poussant cette idée un peu plus loin, si nous symbolisons le déroulement de la vie d’une personne par une droite, il existe certaines sections de cette ligne chronologique au cours desquelles une personne sera plus sujette au développement d’une dépression que d’autres, certaines communes à l’ensemble de la population, par exemple le vieillissement, d’autres dépendant des événements de la vie de chacun : traumatisme psychologique, succession de traumatismes, ou périodes précédant ou suivant immédiatement un accouchement, suivant le déclenchement de la ménopause ou en correlation avec des maladies somatiques, comme le diabète ou le cancer.

Le temps joue également un rôle avant que la dépression ait été formellement identifiée en tant que telle. Malgré l’existence de systèmes de santé adéquats dans de nombreuses régions du monde, le délai entre la survenue des premiers symptômes dépressifs et le diagnostic est souvent considérable. Le temps est également un problème après le diagnostic, lorsque le patient est sous traitement, dans la mesure où le délai d’amélioration des symptômes dépend d’une période de latence qui est généralement de 4 à 6 semaines avant qu’une amélioration ne soit observée, et ceci en dépit du fait que les traitements pharmacologiques et psychologiques s’améliorent constamment et fassent preuve d’une efficacité et d’une tolérance toujours plus importantes. Aujourd’hui, un délai d’action rapide est devenu un indicateur de performance essentiel pour les antidépresseurs — à la fois comme critère répondant aux attentes des patients, mais également comme objectif de recherche pour développer de nouveaux agents possédant un délai d’action plus rapide.

Cet aspect a des conséquences médico-économiques majeures évidentes : l’étude STAR*D (Sequenced Treatment Alternatives to Relieve Depression, Alternatives Thérapeutiques Séquencées pour Soulager la Dépression) a montré qu’un soulagement symptomatique précoce constituait un facteur de prédiction positif d’une rémission. L’amélioration de l’efficacité du traitement soulagera par conséquent le fardeau de la dépression avec le temps, à la fois pour le patient, mais également pour la société.

De Leval postule une « dépression phénoménologique » liée à la perception d’un décalage entre un passé heureux et un présent douloureux. « Plus le fossé entre le passé et le présent est important, plus la dépression phénoménologique est profonde ». Dans la théorie de de Leval, la qualité de vie est perçue comme le décalage qui sépare l’expérience actuelle des aspirations futures, et elle est définie comme « l’adéquation entre les aspirations futures et le présent » ou « la réalisation du futur dans le présent ».

L’impact de la dépression sur la qualité de vie devient encore plus clair lorsque l’on essaie de quantifier la qualité de vie. Les « années perdues pour cause d’incapacité » (AVI) constituent une mesure de l’équivalent en années de vie saine perdues pendant la période au cours de laquelle la santé était dimi-
nuée, et permettent de quantifier de manière statistique la diminution de la qualité de vie par la quantité de temps perdue. La somme de toutes les années de vie caractérisées par une diminution des capacités pour toutes les personnes souffrant d’une affection particulière, pondérées selon la « pondération d’incapacité » particulière de la pathologie, permet de définir un total d’AVI pour cette maladie.

Dans ce numéro de Medicographia, plusieurs auteurs renommés exploitent ces concepts et ces aspects liés au temps en tant qu’entité significative dans la dépression, et les abordent sous différents angles :

- Les caractéristiques temporelles de la dépression selon une perspective épidémiologique constituent le sujet de la contribution de H. U. Wittchen et S. Uhmann, qui décrivent les aspects et les facteurs de risque de la pathogenèse de la dépression.
- G. M. Goodwin aborde le sujet du temps au cours du déroulement de la dépression, les aspects concernant la prédiction de futurs épisodes, ainsi que le moment et la durée du traitement.
- P. Gorwood examine le temps subjectif et la perception du temps chez les patients déprimés, ainsi que leurs conséquences thérapeutiques.
- H. J. Möller, F. H. Seemüller et M. Riedel réfléchissent sur les aspects objectifs du temps et leur importance dans la dépression, mais également sur le problème posé par les antidépresseurs dont le délai d’action est lent, alors qu’il est établi qu’une amélioration précoce constitue un facteur de prédiction de réponse et de rémission.
- G. Hajak et M. Landgrebe développent le concept linéaire du temps en explorant les rythmes circadiens et leur rôle dans la dépression, qui va au-delà de la variation d’humeur diurne observée chez les patients déprimés.
- Le pont entre le temps et les horloges sera jeté par D. Tardito, G. Racagni et M. Popoli, qui présentent la pharmacologie de l’horloge interne et la régulation des rythmes circadiens au niveau intercellulaire et intracellulaire.
- C. Muñoz décrit l’efficacité de Thymanax, le premier antidépresseur mélatoninergique, à chacune des phases de la prise en charge de la dépression et sur leur ensemble, en se basant sur la resynchronisation des rythmes circadiens.
- Dans la section « Question à Controverse », un groupe d’experts discutent du temps sous l’angle de la rapidité du délai d’apparition de l’efficacité des antidépresseurs.
- P. Lemoine aborde le problème des rythmes sociaux dans la dépression au cours d’une interview, en montrant comment les mesurer, comment leur resynchronisation peut apporter un soulagement des symptômes, et comment cet objectif peut être atteint.
- S. H. Kennedy, P. Giacobbe et S. Rizvi décrivent les critères de mesure d’un délai d’apparition rapide de l’efficacité dans le traitement de la dépression.
- Enfin, B. Saletu, P. Anderer et G. M. Saletu-Zyhlarz montrent comment les progrès de l’imagerie médicale nous permettent de visualiser, et par conséquent de mieux comprendre, les effets des antidépresseurs sur le cerveau.
A number of the characteristics of depression are known to vary over time. A full and comprehensive epidemiological characterization of the temporal characteristics of depression is, however, lacking. In this paper, we discuss the methodological challenges and provide a selective review of recent epidemiological evidence covering the following issues: (i) prevalence of major depression by age and gender; (ii) patterns of incidence by age of onset and birth cohort; and (iii) number and duration of major depressive episodes. We also discuss vulnerability and risk factors influencing the temporal characteristics of depression, and comment on cohort trend findings that suggest that there has been an increase in the rate of depression over time. One can conclude that despite the relatively stable pathoplastic structure of depression, there is epidemiological evidence of considerable variability in the onset, episode frequency, and duration of depression over the lifespan. An early onset in youth is associated with a greater frequency of depressive episodes of mostly shorter duration compared with depression with an older age of onset. Depression in old age is associated with considerably greater persistence, as indicated by high proportions of long episodes (>51 weeks) and chronicity. We also confirm the existence of substantial birth cohort effects, and a shift of first onset of depression to a younger age. Overall, this suggests that the rates of major depressive disorders are increasing.

Several salient characteristics of depression vary over time. This is reflected, for example, in the typically episodic nature of major depression and the relevance of biological rhythms in its etiology (manifest, for example, as sleep pattern disturbance), but also in our heavy reliance on the characteristic duration and persistence of depressive symptoms in the differential diagnosis and when separating clinical depression from normal mood variations. The importance of temporal issues is also evident when considering the incidence patterns of depression over the lifespan of males and females, and the associated variation in terms of number and length of episodes and risk factors. Despite numerous epidemiological studies, our current understanding about the timing of depression remains fragmented and incomplete.

Several critical issues can be held responsible for this deficit: (i) few studies have ever attempted a comprehensive epidemiological characterization of depression across the lifespan, including number and duration of episodes; (ii) temporal aspects...
How frequently does depression occur over the lifespan?

Point (1-month), 12-month, and lifetime estimates for depression are mostly studied in isolation, and interactions with developmental risk factors are rarely addressed; (ii) methodological factors, such as reliance on retrospective cross-sectional studies, sampling, age group composition and power, differences in diagnostic assessment tools used, and other factors (somatic factors, secular trends, etc) make the aggregation of findings difficult; (iv) the determination of age of onset and number and duration of episodes depends on retrospective accounts from patients, which are subject to recall bias, current mood state, other comorbid conditions, as well as birth cohort effects; (v) the interpretation of depression findings is further complicated by the possibility that secular trends might exist; that is, younger birth cohorts might have a substantially higher risk of experiencing depressive episodes and suffering from depression at an earlier age than older birth cohorts. This could be relevant, because an early onset of depressive disorders has been shown to be a risk factor for more frequent and longer episodes; and (vi) there is no general agreed strategy on how to define the onset and offset of episodes. From a broader dimensional view, critical questions arise, such as: should onset be defined as the point in time at which all diagnostic criteria for a particular depressive disorder are met, or should subthreshold expressions that might precede or follow the episode—when dealing with duration—also be taken into account? And if yes, how much symptomatology would be regarded as sufficient? Because of the substantially greater difficulties with such broader concepts, this article will concentrate mainly on major depression and major depressive episodes (MDE), for which firmer evidence is available.

Against these mostly methodological caveats, we will provide a selective review of recent epidemiological evidence covering the following issues: (i) lifetime and current estimates for major depression by age group and gender; (ii) patterns of incidence by age of onset and birth cohort; and (iii) characteristics of duration and course. Furthermore, we will discuss vulnerability and risk factors influencing the temporal characteristics, and comment on cohort trend findings.

**Lifetime and current estimates of major depression**

- **How frequently does depression occur over the lifespan?**

An abundance of epidemiological research over the past decades throughout the world has provided evidence that depressive disorders and major depression are much more frequent than was thought in the early 1980s and before. Believed to be relatively rare disorders with cross-sectional rates of 1%-2% and lifetime rates of 4%-5% in the pre-Diagnostic and Statistical Manual of Mental Disorders (DSM)-III studies, increasing and substantial evidence from most studies in the 1990s suggested that major depression and MDE are in fact much more frequent, especially when considering rates of 12-month and lifetime depression. Figure 1 clarifies the different time period references for these rates, ranging from point prevalence (1 month) to lifetime risk.

In a previous review, Wittchen et al reported a median point prevalence of major depressive disorder from studies up to the early 1990s of 3.1 (1.5-4.9), a median rate of 6.5% (2.6%-9.8%) for 6-month and 1-year prevalence, and 16.1% (4.4%-18%) for lifetime rates in the community. These data also suggest that we can estimate that up to a high age, the “true” rate of major depression is likely to be above 21%. The differences between fairly low point and high lifetime rates also underline that major depression is an episodic disorder. It is noteworthy that these estimates are conservative, because subthreshold (prodromal or residual) and successfully-treated depressive patients are not considered! This review also explained the higher estimates in more recent studies, which use increasingly more sophisticated depression assessment methodologies that probe more intensively for the presence particularly of past episodes and the existence of cohort effects. Cohort effects suggest that depression rates have been increasing over the last decades due to increasingly higher rates in more recent birth cohorts compared with older cohorts.
Depression rates and age of onset

Concentrating on MDE in adults (18-65+ years of age), the most recent US National Comorbidity Survey-Replication (NCS-R) found—by and large consistent with the most recent studies in the European Union—that the lifetime prevalence of MDE is 22.9% in females and 15.1% in males (Figure 2A).

Rates are highest in the age group 35-49 (females 26.7%, males 18.6%), and are dramatically lower among subjects aged 65+ (females 13.0%, males 5.3%). Interestingly, the youngest age group reveals only marginally lower lifetime rates compared with the older groups. 12-month prevalence rates (Figure 2B) are about half the rates for lifetime, revealing similar patterns for age and gender. These findings are counter-intuitive at first sight: first, there are high rates even among the youngest age group and there is only a small difference with regard to the age group 35-49, typically assumed to be the high-risk phase and the age group mostly frequently seen in in-patient and outpatient settings. Second, the considerably lower lifetime rates in the elderly appear to be inconsistent with the perception that rates of depression in the elderly should be higher, and not lower, because of their considerably longer time period at risk for major depressive disorder, and because of other factors (see later).

High prevalence and incidence risk in childhood and adolescence?

Carefully conducted prospective longitudinal studies all come to the same conclusion: major depressive disorder and MDE, although rare in children (age <10 years) of both sexes, are already quite prevalent in adolescence, a time period during which the gender difference becomes apparent. Figure 3 displays this gender differentiation using data from birth to the mid 30s from the prospective-multiwave Early Developmental Stages of Psychopathology (EDSP) study. The curves reveal a higher estimated cumulative incidence (35.6%) for first onset in females at age 33 years than for males (23.1%). Most cases with MDE emerged between the ages of 12 and 25 years, with a significant gender difference apparent at around age 14 years. Both males and females showed continued new onsets of MDE after the age of 25 years, suggesting continued, though attenuated, incidence rates over the
lifespan. The consistent evidence of high depression rates in adolescence and young adulthood, along with similar or even stronger evidence for substantial impairment, disability, and treatment rates associated with young age depression, leaves little doubt that the high community estimates in the young describe clinically meaningful depression.

**Low rates in the elderly?**

The substantially lower rates for the elderly are puzzling and have prompted the search for reasons for this finding. Initially, research suggested that the diagnostic instruments were not valid and were inappropriate for older adults, with authors suggesting a series of modifications in order to account for different response styles in the elderly. However, these adaptations did not result in substantial increases in subsequent estimations. Kessler et al also excluded the possibility that recall failure accounts for the difference, by showing that the estimate ratio for subjects aged 65+ is lower for both 30-day and 12-month estimates (31%-32%) than for lifetime prevalence. This gradient suggests that recall error is not responsible for the lower prevalence among the elderly. Recall error, as suggested by Simon and vonKorff, would produce an opposite pattern. Related observations are that the ratio of 12-month prevalence to lifetime prevalence is consistently lower for younger subjects aged 65+ (22%-28%) than in younger respondents (37%-57%), depression in the elderly is more frequently “clinically mild” (21.8% vs 8.2% in 18-34 year olds, 6.8% in 35-49 year olds, and 10.3% in 50-64 year olds), and is associated with a significantly lower degree of severe role impairment and a lower number of days out of social role because of depression. Consistent with some previous research, these findings suggest that community rates of major depressive disorder and MDE in the elderly reflect some lowering of risk, and protective factors all reflect aspects of the older adult’s position in the lifespan. Further, there is some consensus that late-onset depression in old age has distinctly different risk factors (eg, increased rates of vascular, including cerebrovascular, disorders) and presentation (eg, decreased rates of cognitive-affective symptoms of depression and increased sleep disturbance) than earlier-onset depression. In this context, a number of old age depression variants have been suggested: for example, “vascular depression executive dysfunction syndrome,” “depression without sadness” or “depletion syndrome,” Parkinson’s Disease Depression, or Alzheimer’s Disease Depression. Yet none of these concepts has received wider acceptance. Furthermore, there is little evidence from psychometric explorations that the structure of depression in the elderly is overall significantly different from that seen in younger age groups.

**Phenomenology**

Depression in old age differs both in subtle and obvious ways from depression earlier in the lifespan. Presentation, etiology, risk, and protective factors all reflect aspects of the older adult’s position in the lifespan. Further, there is some consensus that late-onset depression in old age has distinctly different risk factors (eg, increased rates of vascular, including cerebrovascular, disorders) and presentation (eg, decreased rates of cognitive-affective symptoms of depression and increased sleep disturbance) than earlier-onset depression. In this context, a number of old age depression variants have been suggested: for example, “vascular depression executive dysfunction syndrome,” “depression without sadness” or “depletion syndrome.” Parkinson’s Disease Depression, or Alzheimer’s Disease Depression. Yet none of these concepts has received wider acceptance. Furthermore, there is little evidence from psychometric explorations that the structure of depression in the elderly is overall significantly different from that seen in younger age groups.
Increased resilience

Since most older adults experience disability, pain, and bereavement and have age-related changes in immune, neurological, and other biological systems, there has been some research into resilience factors that might explain why the elderly less frequently report experiencing depression. As summarized by Fiske et al\textsuperscript{26} and Hendrie et al,\textsuperscript{44} three groups of explanations have been suggested as representing depression buffers (Figure 4): (i) the perceived importance of resources like socioeconomic status, remaining cognitive function, and health; (ii) life experiences that have taught older adults psychological strategies and ways to use social support and manage the stress; and (iii) the role of meaningful engagement, whether in social activities, volunteer work, or religion.

To conclude, none of the current explanations fully accounts for the observed low depression rates in older adults. The preponderance of current evidence indicates that at least major depressive disorder is less common in old age, while clinically significant subthreshold depression, which can also be consequential and is treatable,\textsuperscript{45} might be quite common.

Number of episodes and duration

With very few exceptions,\textsuperscript{5,46-49} most studies merely report rates of MDE by age group, but do not specify frequency and duration. Thus, even the proportion of single versus recurrent episodes, or chronic versus episodic depression, remains frequently unreported.

Kessler et al\textsuperscript{5} report a mean age of onset of 26.2 years for a first episode of MDE, with the lowest age of onset for 18-34 year olds (mean 17.8 years) and substantially higher ages for subsequent age groups (35-49 age group, 25.5 years; 50-64 age group, 33.1 years; 65+ age group, 43.0 years). Among cases with recurrent depression, the mean number of MDE was 18.6 overall, with the lowest number among the young (18-44 years, 15.4 episodes) and the highest for the elderly (30.2 episodes). Spijker et al\textsuperscript{48} reported a median duration of MDE of 3 months in the community. A total of 50% of the participants recovered within 3 months, 63% within 6 months, and 76% within 12 months, and nearly 20% were not recovered at 24 months. Determinants of persistence of the episode were severity of depression and comorbid dysthymia; recurrent depression typically had a shorter episode duration. This is by and large in agreement with a more fine-graded analysis\textsuperscript{50} based on a total of 736 DSM-IIIR MDE cases from the general population. Considerable birth cohort effects regarding the total cumulative MDE risk and age of onset were found (Figure 5), suggesting that the number of episodes and their duration might be different by birth cohort. Overall in this analysis, 53% reported only one episode, while 17.4% had 2-3 episodes, and 29.6% had 4 or more episodes (Figure 6A, see page 120).

The proportion of cases with one single episode of MDE declined fairly consistently from 67.9% in those with less than 10 years at risk, to 46.2% among cases with 40-50 years at risk. Conversely, the proportion of those with 2-3 episodes increased from 9.5% to 19%, and for those with 4+ episodes from 22.7% to 34.7%. This finding is in agreement with a similar analysis recently reported for patient populations by Coryell et al.\textsuperscript{51} What is remarkable though, is that the oldest group with the longest period at risk for depression also revealed a higher proportion of single episodes, suggesting a substantial number of new-onset cases in old age.

In terms of episode duration, overall, 39.6% had short episodes (2-5 weeks) and 17% had an intermediate length of 6-20 weeks (Figure 6B). The majority of cases of MDE reported an episode duration of more than 21 weeks, and chronic depres-
The timing of depression: an epidemiological perspective – Wittchen and Uhmann

A new dimension in antidepressant efficacy

Figure 6. Number of depressive episodes (A) and episode duration in weeks (B) among community cases with lifetime major depressive episode (MDE) by years at risk.

- Family genetic factors

There is consistent evidence from family studies that parental depression substantially increases the risk of the offspring also developing depressive episodes. Such studies have also included examinations of the familial aggregation of recurrence risk and duration of key symptoms. Meta-analyses of family, twin, and adoption studies reveal that the risk of recurrence of major depression is the measure with strongest empirical support for familial aggregation, while evidence for duration is less convincing. However, it should be noted that there is little diagnostic specificity. That is, familial anxiety, substance use disorder, or other mental disorders have often been found to be as important as depression or other mood disorders in predicting depression.

A particularly informative community study in this respect was carried out by Lieb et al., who prospectively studied the longitudinal risk of depressive episodes in 3021 offspring over the first three decades of life by parental mental disorder status, assessed by independent diagnostic interviews. Offspring of...
depressed mothers (odds ratio, 2.9) and depressed fathers (odds ratio, 3.0) were at substantially increased risk of also developing depression up to age 28. The effects were more pronounced when both parents had suffered a lifetime episode of depression and were also elevated in comorbid anxiety disorders. Particularly noteworthy was the finding that parental depression shifts the age of onset of depression in childhood significantly forward. Furthermore, affected offspring had an increased risk of recurrent episodes (among those with non-affected parents the mean number of recurrent episodes was 2.7, among those with affected parents it was 5.2; odds ratio, 1.8), and persistent depression (9 weeks versus 30 weeks; odds ratio, 4.5).80

◆ Childhood and developmental adversities, life events and disasters

Retrospective assessment in cross-sectional studies has shown that childhood adversities, including traumatic events, are significant predictors of an increased prevalence of depression and earlier age of onset. Intercorrelations between different types of childhood adversities make it difficult to pinpoint any particularly important type of adversity.13 More recent prospective longitudinal studies have also highlighted the particular caution that is warranted if using only retrospective designs.14 By comparison with childhood adversities, more specificity has been found in the effects of stressful life events and their relationship to depression.66 Stressors involving loss are more strongly related to depression, while stressors involving threat and danger are more strongly associated with anxiety, and stressors involving both a combination of danger and loss are related to comorbid presentations and higher levels of persistence.65,71,72 There are also important associations with lack of social support73 as well as familial and genetic elements.63 The effects of life events in women seem to be slightly more pronounced than in men across all ages,74,75 suggesting one potential reason for the gender difference in prevalence. The relationship between life events and first onset76 and remission77,78 appears to be stronger than for successive recurrent episodes, which seem to be less dependent on external triggers.79 These findings, however, might be dependent on the type of life event or stress assessed; chronic stress seems to be more relevant for the first episode, and acute stress and an interaction of chronic and acute stress80 might foster recurrent episodes.81 The complex interplay with neurobiological factors in this respect has been recently highlighted by Caspi et al,82 Moffit et al,83 and Zimmerman.84 Revealing that adverse events are particularly pathogenic in individuals with genetic or familial genetic susceptibility.85

Adverse events and chronic life difficulties have also been suggested as an explanation for sociodemographic associations between depression and socially disadvantaged groups, who might have fewer resources to cope with stressful situations. Recently, Kessler et al presented an impressive example of the effect of life events on the risk for mental disorders, and the temporal pattern,86 in a representative sample of prehurricane residents involved in Hurricane Katrina. Contrary to results from other disaster studies in which psychiatric morbidity has typically declined with time, substantial increases in post traumatic stress disorder (14.9% to 20.9%) as well as depressive disorders (10.9% to 14%) over a 2-year observation time were found. Unresolved hurricane-related stresses accounted for large proportions of the intertemporal increases in depression (89.2%).

◆ Effects of comorbid conditions

◆ Mental disorders

The effect of all anxiety disorders88,89 on the onset and course of depression has been well established through cross-sectional88-91 and prospective longitudinal investigations,86,96-97 as well as through clinical studies.86,98 Studies in adolescents and young adults are particularly informative, because this is the high-risk incidence phase for anxiety disorders. Such studies89,100 have demonstrated the substantially and consistently increased risk of subsequent depression, as well as a more malignant course and character of secondary depression.

With some variation according to type of anxiety disorder, up to 50% of all subjects (Figure 7A, page 122) with a primary anxiety disorder have been shown to develop depression, constituting a threefold increased risk of depression. Furthermore, a considerable shift forward in the age of onset of the first episode of depression has been found (see Figure 7B), so that depression occurs earlier. These findings suggest etiologic links between these two types of disorders. Similar, though less consistent, data have also been found for other mental disorders (eg, somatoform disorders,101 substance use disorders100).

◆ Somatic comorbidity

Community studies103 show a close relationship between major depression and physical illness. Evidence for the possibly bidirectional influence of somatic and mental disorders has been provided for such diverse conditions as acute coronary syndromes and depression,104 as well as “disorders of the female reproductive cycle”105-109 for example. Among adults, particularly strong associations were found between chronic disorders and increased risk for MDE, particularly if the disorders involved pain and suffering or major long-lasting restrictions or disability or multimorbidity.82 Chronic diseases and poor general health were particularly predictive of new depressive episodes over a period of 1 year.110 It should be noted though that the relationship is apparently quite complex, since there is no consistent linear relationship between the degree of somatic morbidity and the risk of depression, nor a consistent relationship with aging,2 suggesting that there are also interactions with environmental and biological factors at play.111 Because of the complexity of multimorbidity presentations, there is still insufficient knowledge and data to identify causal relationships and risk factors.112
Age cohort effects: are depression rates increasing?

Given the topic “the timing of depression,” it is almost inevitable that finally one should address the controversial question of whether depression rates are increasing. Examination of the epidemiological evidence leaves little doubt: almost invariably across studies, using a range of different methods, higher overall rates of depression have been documented over time as well as successively younger birth cohorts. Particularly increasing rates in the young have been found, which are associated with a shift forward to younger ages in each successively younger age group. Furthermore, despite proportionally lower rates for the elderly, there is also evidence from recent studies that rates of depression in the elderly are higher compared with those of the 1980s. Thus, why question this trend? At the core of this continued controversy is the question of whether this constitutes a “true” increase, that is, have people in communities around the world “really” become more frequently depressed than 2–3 decades ago? This is almost a philosophical question, because we deal with a theoretical construct measured with imperfect assessment instruments, in studies that are necessarily imperfect as well. Because our understanding of depression, the defining criteria, and our assessment instruments have changed, as has probably the awareness and perception of depression in society, it seems impossible to give a definite answer. Admittedly the meaning of the increasing rates and the cohort effects remain not well understood, and there are other valid concerns that range from methodological concerns regarding the reliability and validity of diagnostic criteria and assessment tools used in the studies, to design and statistical issues inherent in time trend analyses, to speculations about the artifactual nature of such findings, for example with regard to the role of recall failure, response biases, and willingness to report depressive symptoms. However, most of these issues have directly or indirectly been addressed, revealing that none of these factors alone or in combination is able to explain the increase and the cohort effects.

Furthermore, the demonstration of increasing rates is consistent with a broad range of external indicators, such as increased rates of depression in mental health care and primary care institutions, substantially higher rates of children and adolescents receiving treatment, increased rates of suicide attempts, and substantially increasing disability burden due to depression. Assuming that such cohort effects and increases exist, there are tremendous implications for the future. For example, the higher rates and the shift to an earlier age of onset in younger birth cohorts can be expected to be associated with an increasing risk for recurrent episodes and increasingly longer and chronic episodes over the lifespan. In addition, given the continued increase in life expectancy in most countries, one can anticipate a continued high—and even increasing—global societal burden, and a substantial challenge for the mental health field.

References

Elapsed time plays a key role in defining the diagnosis and course of single and recurrent episodes of major depression, treatment responses, decisions to change interventions when treatments fail, and outcomes. There is a certain symmetry in this when looked at from the patient perspective, since recurrent and chronic depression steal significant fractions of the lifetime of individual patients. In reflecting back on time spent depressed, patients rarely regard it as time well spent."

It can be argued that major depression is important because of the time it steals from people’s lives and the disability or burden of disease that it therefore imparts. The appearance, disappearance, and recurrence of depression occupy a central position in defining the disorder. Accordingly, the domain of time is central in the diagnosis of major depression, its prognosis, and its tendency to recur often over a lifetime.

The very long time constants that seem to be involved in the condition are still poorly understood, but they clearly have implications for our understanding of the neurobiology and finally for the treatment strategies that we currently adopt in trying to overcome individual episodes of depression. These aspects of time and depression will be the focus of this article.
**Diagnosis**

Major depression is conventionally defined as a collection of depressive symptoms, which, according to the *Diagnostic and Statistical Manual of Mental Disorders Fourth Edition Text Revision* (DSM-IV-TR), must have been present together for at least 2 weeks. The choice of a 2-week cut-off is obviously arbitrary, and if a constellation of depressive symptoms is present for only 2 weeks, such an episode is likely to be of limited clinical significance. Indeed, broadly speaking, the longer symptoms have been present and unremitting, the more confident one becomes of any diagnosis of major depression, the greater the impact it is likely to have on personal, psychological, and social function, and the more important treatment success becomes. It also turns out that the length of time during which an individual has been depressed is a predictor of subsequent outcome. Thus, in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, the duration of illness was an independent predictor of failure to respond to treatment in a large population (over 3000) of index cases of major depression, all treated systematically with citalopram. The STAR*D finding echoes those from other studies showing that the duration of illness may well have an impact that is both statistically and clinically significant. However, the duration of illness that makes this impact is months rather than weeks. Hence the DSM-IV-TR definition of major depression is a relatively liberal one. It is durations of illness of up to 2 years that seem to have the most major impact in lowering subsequent rates of response to acute treatment.

The natural history of a depressive episode in the general population is recovery; symptoms remit, the subjective burden of depression disappears, and objective wellbeing eventually returns. The definition of the phases of this response rests on principles that were established by consensus about 20 years ago. The conventional terms and the time course that they describe are shown in Figure 1. The acute phase of depression is seen as requiring some form of acute treatment. For reasons of space, the episode is shown schematically as having a very recent onset, although in practice this is a little unlikely, as will be clear from the preceding discussion. Treatment will hopefully facilitate early response, which is often defined as a 50% reduction in symptoms (the point where the solid line in Figure 1 crosses the broken axis). Response rates allow comparisons between different early acute treatments. Response is followed by a continuing reduction of symptoms to a point defined as remission (usually a level of symptoms defined by a fixed point on a rating scale like the Hamilton Rating Scale for Depression [HAM-D]). However, remission takes time, and many acute placebo-controlled studies are kept short to enhance patient retention.

Response rates have significant limitations if one wishes to extrapolate research findings to expected clinical benefits. It has been argued more recently that remission is the key objective, and should thus be the primary outcome in short-term treatment studies.

"Time course" is a term used in defining other terms relating to the phases of treatment and the nature of any return of symptoms. From the point when a patient reaches remission, it is conventional to describe the treatment phase as "continuation" for the next 8 weeks, and "maintenance" after that point. Continuation is the phase following remission when treatment should always be continued and further reduction in symptoms should hopefully be seen. Maintenance is continuation of treatment beyond full recovery to a phase in which the treatment is conceptualized as preventing new episodes of illness in the longer term. Its duration may be indefinite, but most guidelines recommend at least 6 months.

Symptoms returning within the acute and continuation phases are described as relapse (of the original index episode), and those occurring after recovery (in the maintenance phase) are defined as a recurrence (and notionally as the appearance of a new episode). These ideas imply that there is some...
thing unitary about a depressive episode, and that once it has gone away, the patient moves into a different state of risk and perhaps a different state of neurobiology. Thus, in effect, the treatment of a single episode can be thought of as taking place within a finite period of time. Whether this is actually true is not yet known, and indeed it is doubtful as to whether we yet have the measures that would necessarily allow us to know whether it is true. However, it is a potent hypothesis and a useful one. While it is now enshrined in our terminology, as shown, we should regard it as provisional, seek better understanding of what actually determines patterns of symptom response and remission, and be prepared to change our terminology if it does not correspond to the facts.

**Prognosis and recurrence**

Repeated episodes of illness are frequently similar clinically, but they show potentially different temporal patterns. Long-term study of severe episodes of depression requiring admission to hospital has shown that patients with unipolar depression tend to have characteristic rates of relapse, with rather different probabilities of recurrence after repeated episodes such that the probability of further illness is increased with each successive episode (see Figure 2). In unipolar disorder, neuroticism, female gender, and/or early abuse and neglect. These factors seem to be translated into depressive episodes by the moderating effect of adversity, either in the form of acute life events or chronic difficulties in the face of which patients may develop episodes of clinical depression. The excess of depressive episodes usually reported in women was associated in a study by Kendler et al with depressive episodes in the context of low stress, but this finding requires confirmation. Most available twin data comes from women, although a parallel series of studies is also emerging for men. There are minor differences and, in particular, the genetic overlap between neuroticism and major depression in men may be greater than in women. However, there is broad convergence in the apparent causes of major depression between both sexes.

The pattern in women is best established for first episodes of depression, for which life events that apparently “trigger” the episode are a relatively common observation. They become less obvious for recurrence in individual patients, suggesting that in some sense, patients become primed to depression and therefore more likely to develop an endogenous pattern of illness as time goes by. Expressed another way, with recurrent episodes of major depression, the role of environmental stressors progressively diminishes. Proving that this occurs and determining its naturalistic properties requires control of a variety of confounding factors and has been best addressed in female twins. With increasing numbers of previous episodes (up to approximately 10 episodes), the association between life events and new depressive episodes fell approximately linearly. More than 10 previous episodes had little additional impact.

The nature of this process—sometimes described as kindling—is poorly understood. It has been suggested that differences between individuals with high and low genetic loading may be that to be highly loaded means to start with a greater degree of priming for the onset of a first depressive episode. Whether a priming or kindling effect is a useful heuristic idea will depend upon developments in our understanding through neurobiological studies. In young people with a family history of depression but no personal history of a depressive episode, there is evidence of increased cortisol secretion and impaired modulation of the anterior cingulate cortex in response to emotionally valenced stimuli. There is also evidence that similar emotional biases can be detected in those with high neuroticism (and no family history) when studied at an early age before any personal history of mood disorder. However, interestingly, changes in cortisol secretion appear to be confined to subjects with a family history of depression at that age.

**Figure 2. Time to recurrence of major depressive disorder as a function of number of previous depressive episodes.**


The times to re-admission to hospital tend to be longer than for bipolar patients in the same clinical population. Although beyond the scope of this article, the differences (and similarities) between bipolar and unipolar depression are of great current interest.

The process whereby an individual first episode is triggered and subsequent episodes develop remains of great interest. Most first episodes tend to be preceded by a set of identifiable risk factors. Those that confer vulnerability relate to family history of depression, personality (anxious worrying/high neuroticism), female gender, and/or early abuse and neglect. These factors seem to be translated into depressive episodes by the moderating effect of adversity, either in the form of acute life events or chronic difficulties in the face of which patients may develop episodes of clinical depression. The excess of depressive episodes usually reported in women was associated in a study by Kendler et al with depressive episodes in the context of low stress, but this finding requires confirmation. Most available twin data comes from women, although a parallel series of studies is also emerging for men. There are minor differences and, in particular, the genetic overlap between neuroticism and major depression in men may be greater than in women. However, there is broad convergence in the apparent causes of major depression between both sexes.
There is also evidence that patients who have had an episode of depression and who have fully recovered show abnormalities in their underlying neurobiology. The most impressive demonstration, which links mood regulation directly to serotonin metabolism, is the precipitation in a matter of hours of a depressive syndrome as a result of tryptophan depletion. Such patients with a previous history of depression can also be challenged with a less severe depletion of tryptophan. Under these circumstances, there is no recurrence of any depressive symptoms, but there are differential effects on cognitive function compared with age-matched controls, with differential effects in the patient group for the amplitude of startle responses, episodic memory, and recognition of happy facial expressions. These changes suggest a dysregulation in emotional processing and memory function following acute reduction in serotonin function. These changes could represent the pathways in mood dysregulation per se. They were not, in this case, sufficient to cause a mood change.

While implicating serotonin directly, these findings do not of course exclude a contribution from other neurotransmitter systems in mediating different components of the depressive syndrome that remain incompletely understood. Reduced systems in mediating different components of the depressive syndrome as a result of tryptophan depletion. Such patients with a previous history of depression can also be challenged with a less severe depletion of tryptophan. Under these circumstances, there is no recurrence of any depressive symptoms, but there are differential effects on cognitive function compared with age-matched controls, with differential effects in the patient group for the amplitude of startle responses, episodic memory, and recognition of happy facial expressions. These changes suggest a dysregulation in emotional processing and memory function following acute reduction in serotonin function. These changes could represent the pathways in mood dysregulation per se. They were not, in this case, sufficient to cause a mood change.

Major depression is a recurrent disorder, and over a period of many years may have a major impact on the lives of individuals simply by virtue of the impact of chronic or recurrent symptoms, which are socially and personally incapacitating. However, in addition, it is now understood that depression has an impact on simple memory performance, which is also potentially cumulative with episode recurrence and may contribute to a professional disability and difficulties in employment. Cognition as an end point in the treatment of depression is a new concept, but one that seems set to assume increasing importance. The time spent depressed during multiple previous depressive episodes in the clinical history seems to be an important predictor of minor, but nevertheless significant, cognitive impairment following recovery from individual episodes.

**Treatment guidelines for single depressive episodes**

As already indicated, chronicity of the depressive episode predicts reduced responsiveness. It suggests that long delays in treatment are highly undesirable. On the other hand, short delays may make rather little difference, and for that reason, the UK National Institute for Health and Clinical Excellence (NICE) guidelines have recommended that for patients with minor levels of symptoms and relatively short histories, a time of watchful waiting may allow recovery without the need for active intervention. How effective this approach may be has not been addressed in effectiveness studies, but is simply derived from a consideration of first principles. It may be appropriate in health care systems with relatively easy access to primary care services, but it requires clinical vigilance and not neglect.

Long-term watchful waiting is clearly not likely to be a helpful strategy, and escalation through a system of stepped care to further treatments, either with effective psychotherapy or antidepressants, is the recommendation of almost all guidelines. The recommendations from NICE are summarized in Figure 3. The particular choice of antidepressant is not dictated overwhelmingly by weight of evidence favoring one treatment over

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**Figure 3.**

Summary of the UK National Institute For Health and Clinical Excellence Stepped Care model for depression treatment.

another, although on average, some antidepressants are probably more effective/well tolerated than others. Head-to-head studies can be aggregated to allow meta-analysis, and a recent study suggested that published data favors, for example, sertraline compared with reboxetine. However, many other factors other than clinical evidence influence the first choice, from simple economics to patient preference.

**Next step treatments after failure of an initial drug treatment**

Treatment failure is not uncommon in a major depressive episode. Time is again an important determining factor in clinical decision-making. How long one should wait before failure is declared has not been established, and is perhaps always a complex clinical decision. Careful analysis of early time points in clinical trials has shown that improvement comes relatively early, and so, in principle, early decisions about treatment benefits (at 2 weeks, perhaps) may be possible. However, as with other aspects of clinical judgment in mood disorders, the greater the time that elapses, the greater the confidence in the clinical decision, and many guidelines have advocated waiting 4 or even 6 weeks before making a change. STAR*D was originally designed to guide the next treatment step after the failure of a selective serotonin reuptake inhibitor (SSRI; citalopram). Unfortunately, the randomization steps were largely subverted by planned patient preference options. There is a lack of direct evidence on the comparative efficacy of a range of next steps after initial treatment of a single episode has failed.

The treatment options are as follows (broadly taken from the British Association for Psychopharmacology [BAP] Guidelines 2008, which should be consulted for more detailed justification). Since there is a relative dearth of compelling evidence for one strategy over another, guidelines may produce rather different recommendations if attempts are made to concoct an algorithm to anticipate particular successive preferences. STAR*D provides an interesting example of just such an over- clinically supported after more than one SSRI failure. The treatment options are as follows (broadly taken from the British Association for Psychopharmacology [BAP] Guidelines 2008, which should be consulted for more detailed justification). Since there is a relative dearth of compelling evidence for one strategy over another, guidelines may produce rather different recommendations if attempts are made to concoct an algorithm to anticipate particular successive preferences. STAR*D provides an interesting example of just such an over- clinically supported after more than one SSRI failure.

**Switching to a different antidepressant**

Switching to another antidepressant is probably the commonest approach, including switches within the same class. There is some evidence for enhanced efficacy with venlafaxine after switching from an SSRI. The potential for pharmacokinetic or pharmacodynamic interactions requires care in some circumstances. For example, a switch from monoamine oxidase inhibitors to serotonin reuptake inhibitors may provoke the serotonin syndrome. Where possible, recommended protocols should be followed to minimize risks.

Switching is worth consideration when there is poor tolerability as a result of significant side effects or no improvement on careful clinical assessment. The switch options include antidepressants of a similar class (sometimes recommended as the simplest first option), followed by a different antidepressant class after a second failure within a class. Venlafaxine is specifically supported after more than one SSRI failure.

**Augmentation of the ineffective antidepressant**

There is evidence for the efficacy of augmentation of antidepressants with lithium, olanzapine, risperidone, quetiapine, and aripiprazole. Aripiprazole appears to be the most promising of these. Tri-iodothyronine also has adherents, as does mirtazapine, tryptophan, methylphenidate, lamotrigine, modafinil, antiguocorticoids, and estrogen (in perimenopausal women), although more specialized combinations probably require expert supervision. Augmentation may be logically preferred when there has been a partial/insufficient response to the current antidepressant, but with good tolerability, or when switching antidepressants has been unsuccessful.

**Psychological treatment options**

Addition of cognitive behavioral therapy to ongoing antidepressant treatment may be effective, but requires significant therapist expertise. Adding other psychological or behavioral treatments that have established acute treatment efficacy may also be merited.

**Physical treatment options**

Electroconvulsive therapy should be considered in more severely symptomatic patients in whom two or more treatments have failed. Electrode placement affects both efficacy and adverse effects on memory (which are probably positively correlated). Unilateral treatment is often preferred as first-line treatment.

Vagal nerve stimulation is an option for patients with chronic treatment-resistant depression, as is deep brain stimulation and even ablative neurosurgery. A full discussion of who could be considered eligible having proved refractory to pharmacological and psychological treatment, is beyond the scope of this article.

**The long term**

In addressing treatment, the objective is to enable the patient to achieve remission and a full recovery within at most 3-4 months, and to continue treatment for at least 6 months.
Given the strong evidence of relapse prevention in studies that, for regulatory purposes, have been designed to confirm efficacy over longer periods of time, longer term treatment should clearly be considered in patients believed to be at increased risk of recurrence of depression.23

There have been rather few true maintenance studies in which patients have been allowed to recover, then been withdrawn from antidepressants, and then re-randomized to maintenance treatment de novo. The only large example with sertraline again showed a positive benefit reflecting the findings seen in relapse prevention studies.

More conventional relapse prevention studies involve open treatment with a single antidepressant to remission of the acute episode, followed by double-blind continuation or withdrawal (to placebo). Such designs are usually said to enrich the sample for responders to the acute treatment, and so may favor finding a positive effect when treatment is withdrawn. A true maintenance study excludes this effect.

Conclusion

Elapsed time plays a key role in defining the diagnosis and course of single and recurrent episodes of major depression, treatment responses, decisions to change interventions when treatments fail, and outcomes. There is a certain symmetry in this when looked at from the patient perspective, since recurrent and chronic depression steal significant fractions of the lifetime of individual patients. In reflecting back on time spent depressed, patients rarely regard it as time well spent. This implies that a challenge for the future is to reliably shorten all the time periods that are currently too often long and uncontrolled in depression. This means time to diagnosis, time to effective treatment, and most critically time spent depressed.

References


Keywords: time course; depression; treatment duration; response; remission; continuation; maintenance
La « temps » est une caractéristique constitutive importante de la dépression majeure, qu’il s’agisse de son diagnostic, de son pronostic ou de sa tendance à récidiver au cours d’une vie. La dépression majeure se définit habituellement comme un ensemble de symptômes dépressifs se manifestant pendant au moins 2 semaines. Plus les symptômes se poursuivent sans rémission, plus le diagnostic de dépression majeure s’affirme, et plus l’impact de la dépression retentit sur les fonctions personnelles, psychologiques et sociales. Une dépression qui dure de nombreux mois est plus difficile à traiter. Les phases du traitement ont fait l’objet d’une définition consensuelle il y a environ 20 ans. La réponse au traitement se définit comme une diminution de 50 % des symptômes initiaux, cette diminution se poursuivant de façon ininterrompue jusqu’à un point défini comme rémission, habituellement fixé sur une échelle type HRSD (Hamilton Rating Scale for Depression). À partir de la rémission, il est classique de décrire les 8 semaines suivantes comme une phase de « maintien », celle-ci étant suivie par une phase « d’entretien ». Nos connaissances sur la neurobiologie qui sous-tend le risque ultérieur de récidive en sont à leurs balbutiements. Le traitement aigu fait désormais l’objet de nombreuses recommandations cliniques, le problème le plus difficile étant l’étape suivant l’échec d’un premier antidépresseur. La phase de maintien est celle qui suit la rémission, où le traitement doit absolument être poursuivi et où de plus amples réductions des symptômes sont espérées. La phase d’entretien est celle de la poursuite du traitement au-delà de la guérison complète dans le but, conforme aux hypothèses actuelles, de prévenir la prévention de nouveaux épisodes de la maladie à long terme. Sa durée peut être indéfinie, mais la plupart des directives recommandent au moins 6 mois.
Dépression et temps : une perspective épidémiologique

Un certain nombre de caractéristiques de la dépression sont connues pour subir des variations au cours du temps. Il manque cependant une description épidémiologique complète et détaillée des particularités « chronologiques » de la dépression. Dans cet article, nous abordons les problèmes d’ordre méthodologique au travers d’une revue sélective des données épidémiologiques récentes sur les thèmes suivants : (1) prévalence de la dépression majeure par âge et par sexe ; (2) aspects de l’incidence par rapport à l’âge de survenue et à l’année (cohorte) de naissance ; et (3) nombre et durée des épisodes dépressifs majeurs. Nous examinons également la vulnérabilité et les facteurs de risque influant sur les caractéristiques chronologiques de la dépression, ainsi que les tendances évolutives qui se dégagent des études de cohortes, et qui suggèrent que le taux de dépression a augmenté au cours du temps. Il ressort de toutes ces données qu’en dépit d’une structure pathoplastique relativement stable de la dépression, son épidémiologie témoigne d’une variabilité importante dans l’installation des épisodes dépressifs, leur fréquence et la durée de la dépression au cours de la vie. Ainsi, une survenue précoce dans la jeunesse s’associe à une plus grande fréquence d’épisodes dépressifs en général de plus courte durée que ceux intervenant à un âge plus avancé. À l’opposé, chez les personnes âgées, la dépression s’étend sur une durée beaucoup plus longue, comme le montrent des taux importants d’épisodes longs (> 51 semaines) et de chronicité. Nous confirmons par ailleurs l’existence d’effets importants liés à la cohorte d’âge, avec un décalage du premier épisode dépressif vers un âge plus jeune. Au total, les données convergent pour suggérer que les taux des troubles dépressifs majeurs sont en train d’augmenter.

Keywords: depression; age of onset; disease course; risk factor; development; prevalence; rate
Depressed patients and their notion of time

by P. Gorwood, France

Time perception involves different parameters that have cognitive dimensions, such as arousal, attention, memory, and mood. The neurobiological mechanisms of time processing seem to differentiate intervals of milliseconds (which concern motor tuning, and for which the cerebellum is mainly involved), hours and days (which define circadian rhythms, with the suprachiasmatic nuclei being in charge), and seconds and minutes (required for counting and estimating time; a complex fronto-striato-thalamic circuit probably being implicated). Perception of the speed of time is slower in depressed patients, because of abnormal subjective time experience and objective time judgment, and is probably explained by the additive effects of decreased arousal, attention, and memory processes. The possibility of a direct role of mood has also not been eliminated. Abnormal perception of time and decreased speed of the internal clock are both observed in depressed patients, and give a relevant and different insight into major depressive disorder. Although numerous clues are already available (regarding clinical and neurobiological findings), the role, mechanism, and etiology of abnormal time perception in depression has probably not been studied enough.

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“On the wings of time, sadness is flying…”
LA FONTAINE (The young widow, Book VI)

The capacity to analyze and adapt to the temporal parameters of a specific situation is an everyday requirement, and sometimes a life threatening necessity. We usually have to be “on time” for a large number of common activities, but fine synchrony and tuning of motor activity is particularly solicited when running away from major danger...

Time perception is needed at three major levels according to different time ranges
Temporal judgments are constructions of the brain. Defining ranges of time in time perception is particularly important, as the mechanisms seem to differ depending on the time range involved: in the circadian range, the suprachiasmatic nuclei (SCN) of the hypothalamus have a clear role, whereas the millisecond range, which may be more relevant for motor activity, may especially involve the cerebellum (Figure 1, page 134). To give a simple example, eating strawberries at lunch implies that (i) you have perceived that it is around midday; (ii) you took the decision to buy them; and (iii) you are able to transfer each strawberry successfully from plate to mouth.
The feeling in depression that time passes more slowly has received limited attention in the literature,2–9 and has sometimes led to negative results.2,5,7,10 probably because accurately assessing such complex and subjective feelings brings methodological difficulties.

The discrepancies are partly explained by differences in methodology, patients, and aspects of time perception. Nevertheless, as detailed in the next paragraphs, there are six types of evidence that the internal clock of depressed patients is abnormal. Indeed: (i) the subjective feeling of slower time experienced during depression has been detected and replicated; (ii) depressed patients have been found to have more abnormal time judgment than controls for this aspect; (iii) more severely depressed patients are slower than less severe ones; (iv) a significant correlation has been reported between the severity of depression and time estimate abnormalities; (v) when depression improves, time judgment also improves; and (vi) the opposite of depression, i.e., mania, is associated with an increased speed of the internal clock.

**Time perception is abnormal in major depressive disorder**

Subjective time experience can be assessed with a visual analog scale by asking the subject to mark how slow or fast the flow of time is experienced at the moment of investigation. In at least two studies, this has been found to be significantly slower in depressed patients than controls.5,11 After 23 depressed inpatients completed a self-rating questionnaire of time awareness, it was also found that they felt that time passed more slowly than the same number of matched nonpsychiatric controls.5 In another study, when compared with controls, depressed patients indicated on a verbal report measure that they experienced time as passing more slowly.2 Direct questioning about the speed of time is even simpler: this was carried out in a study half a century ago, and a very significantly higher incidence of the slowing down of the experience of time was reported in the depressed state compared with the recovery state.7 Interestingly, at the clinical level, the depressed patients reported a slowing, and some even an apparent stopping, of the passage of time, describing their experiences in evocative terms (“Every hour seems a year to me”; “It is terribly slow–interminable”; “Time? It is standing still”).7

**SELECTED ABBREVIATIONS AND ACRONYMS**

SCN suprachiasmatic nuclei

Figure 1. Time ranges involved in the organization of behavior.

It is not surprising that time perception is a complex entity, as these three events imply the involvement of different time ranges and neurological structures, which one can more or less distinguish (Figure 1). Thus clear-cut distinctions between below-second and above-second time ranges when analyzing the neurobiology of timing may be artificial, and for some authors,1 even misleading. Proposing certain heuristic models and trying to sum up the present knowledge about the neurobiology of timing could be helpful. Nevertheless, from the start, we should distinguish between the different aspects of timing and analyze the different elements that may be involved.

**Subjective time perception is influenced by mood state**

Our emotional state influences the way we feel time is passing. Everybody has experienced the fact that time drags when we are feeling bored or sad, whereas time flies when we are feeling excited or happy.

Major depressive disorder, which may represent a state of extreme sadness, is defined by a series of core symptoms that include a decrease in appetite, sleep, sexual desire, energy, and psychomotor activity. The latter aspect is quoted in nearly all instruments assessing depression, and can be analyzed by a specific instrument (the Psychomotor Retardation Rating Scale). This scale, devoted to psychomotor retardation, includes one item devoted to the “patient’s perception of the flow of time.”

Apart from these clinical aspects, the role of time perception in depression has also been analyzed at the phenomenological and psychopathological levels by Janet and Minkowski. In melancholia, according to Minkowski, time lived is slower and sometimes stops altogether: the present loses clarity, the future is diminished as change seems less and less possible, and the past looms into the present in the form of guilt and regret.
An easy way to assess “time estimation” is to ask a patient to estimate the time length for a task that has a fixed time length. Twenty-five endogenous depressive patients underestimated a 30-second interval by 6 seconds, whereas 12 healthy controls overestimated this interval by more than 10. In another trial, 30 severely depressed hospitalized patients overestimated 160-second, 240-second, 15-minute, and 30-minute time intervals compared with 30 controls. Depressed patients also overestimated time lengths of 12-minute spans compared with controls.

“Time production” is a more proactive compound of time judgment. The subject is asked to produce a certain time span, using active demonstration of, for example, the “go” and “stop” signals. When asked to produce a 35- and 90-second time span, depressed patients were found to produce shorter time lengths (29 and 64 seconds on average) than controls. Grinker et al showed that patients with the most severe form of depression had the shortest estimation of standard durations of 1 and 3 seconds.

Quantitative approaches have also led to relatively homogeneous results. A feeling of being unwell was found to be accompanied by a more pronounced time estimation error. With the temporal bisection task, the higher the depression score, the shorter the signal duration was judged to be. Grinker et al also obtained a significant correlation between the individual depression scores and time estimates in a discrimination task.

In one study, when the depression score improved with treatment, an analog scale assessing subjective time experience tended to normalize. Depressive patients have not only been compared with healthy controls, but also with patients with mania. Interestingly, on a visual analog scale, controls report a balanced experience of the flow of time, manic patients an enhanced experience, and depressive patients a slowed experience of time flow. When assessing time production (giving a “stop” signal when the proposed duration is supposed to be finished), the intermediate position of controls between manic and depressed patients was only observed for a shorter duration (7 seconds), and did not reach statistical significance.

Time perception also involves motor, arousal, attention, and memory processes. Depression has a strong cognitive impact, but the motor components should not be neglected when assessing time perception, especially in the production of time intervals. Indeed, most of the previously described studies were based on a wide range of time lengths, from 1 or 2 seconds, to minutes, and even hours. Furthermore, they frequently rely on temporal judgment, which also requires the production and timing of a motor response (such as tapping or counting). In the knowledge that psychomotor retardation is a core feature of depression, it is difficult to dissociate the role of the motor component from that of the timing component in temporal performance, even though these two components may be related. Indeed, when specifically assessing the duration of movement patterns in depressed patients with melancholia, Lemke et al showed that the median of repetitive movements was higher in depressed patients than in the control group, regardless of the presence or absence of medication.

In order to avoid this confusing impact of motor retardation, a temporal bisection task was tested in depressed patients. In the test, two standard durations both below 2 seconds, one short and one long, are presented to subjects who have to categorize each probe (of variable duration) as being closer to the long or to the short standard duration. With this approach, a shift toward shorter durations, therefore an underestimation of time (i.e., slower internal clock), was observed in depressed patients.

A similar approach in another study initially gave the same type of results, but mainly for long intervals (above 1 second), probably because longer intervals require supplementary cognitive resources.

**A comprehensive model of interval timing**

The “scalar expectancy theory” was initially proposed by Gibbon and was largely developed later. As simplified in Figure 2, this theory is built on the idea of a neuronal pacemaker, which provides repetitive and regular pulses. Pulses are then gated (in order to define the beginning and the end of the duration to assess), and stored as an accumulated value (the number of pulses) in stored memory. The assessment of
the duration of a specific task is then compared with reference memories, leading to a decision. This model was considered to successfully predict the outcomes of a large proportion of behavioral, pharmacological, and anatomical work in the field. 17

This model of an internal clock has the advantage not only of being simple, but also of involving different cognitive features. Indeed, “gating” means being able to focus attention (with enough arousal) on when to open and close the inputs, “comparing” (the number of pulses that were stored in the accumulator with reference memory) needs encoding and access to memory contents, and “concluding,” ie, giving the stop signal as a consequence of the perception that the correct time interval has been reached, solicits motor skills. On the other hand, the scalar expectancy theory might be more relevant from a mathematical, rather than a neurobiological perspective, mainly because it is difficult to instantiate neural mechanisms that accumulate pulses over the order of minutes. This useful model was thus considered to be a “well-structured metaphor [rather] than a diagram of the working brain.”17

The neurobiology of timing
Initially, patients with a cerebellar pathology were used to pinpoint the role of the cerebellum in timing perception, but evidence has now been enriched with neuroimagery, stimulation, or inhibition using repetitive transcranial magnetic stimulation (rTMS), and electrophysiology data (for a review, see reference 18).

Other neural regions might serve as a dedicated timing system, including the basal ganglia, the supplementary motor area, and the prefrontal cortex. 18 A fronto-striato-thalamic circuit, modulated by the dopamine system, would appear to be crucial for temporal processing within the range of seconds.

The basal ganglia receive the majority of their stimuli from the cortex, the thalamus, and the midbrain, and although initially reported as being involved in motor functioning, are now considered as playing an important role in motivational and cognitive aspects of brain functioning. The cortex projects glutamatergic (excitatory) afferents to the basal ganglia, mainly through the striatum (Figure 3). Striatal γ-aminobutyric acid (GABAergic; inhibitory) outputs project to the internal globus pallidus and the substantia nigra pars reticulata. These two structures provide an inhibitory influence on the thalamus, which, in turn, provides an excitatory output back to the cortex (and partly to the striatum).

Figure 3 was built on a schema usually proposed to describe the loops involved in motor activity (especially regarding the basal ganglia). The main proposed change today is that the output signal from the cortex does not represent motor activity, but the sum of individual waves of neurons that have different frequency oscillating signals. Adding together individual neurons as a model for producing an internal clock has the considerable advantage of allowing production (and recognition) of intervals of seconds or even minutes, which are far above the usual 200-millisecond intervals of neuronal activity. Indeed, mixing three neurons with 5 Hz (a peak every 200 msec), 6 Hz, or 7 Hz oscillating signals will produce a curve at which a peak is observed every second. 17 Such peaks, from milliseconds to minutes depending on the number of neurons concerned and their individual frequency, may then serve as an output signal that will reach the striatum.

In terms of the role of the cortex, according to single cell activity studies, the prefrontal cortex may be more specifically involved. Increasing activity of dorsolateral prefrontal neurons was detected during the delay period of a task soliciting post-
bilateral in the anterior hypothalamus and are entrained to the external light-dark cycle by a neural pathway that transmits light information from the eyes through the retinohypothalamic tract.

Thus the neurobiological circuits for circadian and ultradian intervals seem to be different. Indeed, three types of distinction have been proposed between circadian and shorter interval timing. The circadian clock would be phase-based (automatically generated by the SCN), with low flexibility (the 24-hour basis can be shifted only by 1 hour a day, for example during jetlag) and constant variability, whereas the interval clock would be counter-based (adding pulses), with high flexibility (as relying on internal memory) and scalar variability (implying it has decreased precision for longer intervals).

**Conclusion**

The way we assess the speed of time forms part of our basic cognitive skill set, and is an important part of everyday analyses, decision making, and action. Such a core activity can be (artificially) distinguished according to time intervals. For intervals of below a second, most of the task concerns motor activity and may be more specifically orchestrated by the cerebellum. For intervals of over an hour, a specific structure is shared by many animals, ie, the SCN, allowing species to function both synchronously and in accordance with the night/day rhythm, and therefore to survive. For intervals of seconds to minutes, the timing circuit seems to be more complex, also involving cognitive skills. Whichever way neurons are organized as pacemakers (different models have been proposed, and their validity is difficult to prove), it is interesting that arousal, attention, and memory are involved, because of their ability to influence the inputs or outputs of the pacemaker. It is therefore not surprising that in major depressive disorder, which is known to be associated with poor attention and memory impairment, time seems to pass slower.

The specific impact of emotion has been tested, with analyses (using event-related potentials) of the way subjects react in front of neutral versus sad faces. Under emotional conditions, the P160 and P240 amplitudes have been found to be enhanced, suggesting that intentional bias for emotional stimuli attenuates the cognitive resources for time perception. The important role of dopamine at the neurotransmitter level, and the specific place of the prefrontal cortex in time production, both argue in favor of abnormal time perception belonging to the list of symptoms of depression; or at the least, sharing some identical neurobiological patterns.

**References**


La notion du temps chez les patients déprimés

La perception du temps met en jeu différents paramètres aux dimensions cognitives comme l’éveil, l’attention, la mémoire et l’humeur. Les mécanismes neurobiologiques impliqués dans le traitement du temps semblent capable de distinguer des intervalles de millisecondes (modulation du tonus musculaire, principalement sous la responsabilité du cervelet), des intervalles d’heures et de jours (définissant les rythmes circadiens gérés par le noyau suprachiasmatisque) et enfin des intervalles de secondes et de minutes (nécessaires au comptage et à l’estimation du temps, impliquant probablement un circuit complexe fronto-striato-thalamique). Le temps est ressenti par les patients déprimés comme ralenti, d’une part du fait d’une perception subjectivement anormale de son déroulé, et d’autre part d’un jugement temporel objectivement erroné. Ceci s’explique probablement par les effets conjugués d’une diminution de l’éveil, de l’attention et de la mémoire. En outre, un rôle direct de l’humeur n’est pas écarté. La constatation d’une perception du temps anormale et d’un ralentissement de l’horloge interne chez les patients déprimés, stimule de façon pertinente notre compréhension des états dépressifs majeurs. Cependant, même si notre connaissance s’est enrichie de nombreuses données concernant la clinique de la perception du temps et les mécanismes neurobiologiques potentiellement impliqués, il n’en reste pas moins que le rôle, le mécanisme et l’étiologie de la perception anormale du temps dans la dépression n’ont pas livré tous leurs secrets.
Major depression is still today a devastating illness, currently reflected by the most recent World Health Organization statistic showing depression to be the leading cause of years lost due to disability. Although recent psychopharmacologic developments have resulted in progress, individualized psychopharmacology is in its early stages. One way to individualize treatment is to use predictors such as early response. Today, there is broad consensus among the research community that (i) early changes resulting from treatment of major depression occur within the first 2 weeks of antidepressant treatment; and (ii) they are highly predictive of the later outcome. Nevertheless, this fact is still largely ignored by most treatment guidelines in major depression. This review summarizes current knowledge of the methodological pitfalls in the assessment of early treatment response, discusses actual concepts of possible biological mechanisms involved in early drug response, and summarizes the current knowledge base regarding the potential of today’s available drugs to induce early treatment changes. Moreover, the reasons still contributing to the outdated belief of the delayed onset hypothesis, and the clinical implications, will be discussed.

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apy with an antidepressant compound (without considering subtype and individual psychopathology). After some waiting, and no visible changes after 1 or 2 months, a switch to another medication would follow. In such a “worst case scenario,” this very same procedure might be repeated until the patient remitted spontaneously after another couple of months. The underlying reason for this is the general and not infrequent assumption today that available antidepressant compounds take a minimum of 4 to 6 weeks to unfold their antidepressant properties. This assumption can lead to a certain

<table>
<thead>
<tr>
<th>Disabling condition</th>
<th>High-income countries</th>
<th>Low- and middle-income countries</th>
<th>World</th>
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<tr>
<td></td>
<td>0-59 years 60 years and over</td>
<td>0-59 years 60 years and over</td>
<td>All ages</td>
</tr>
<tr>
<td>1 Hearing loss</td>
<td>7.4 18.5</td>
<td>54.3 43.9</td>
<td>124.2</td>
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<tr>
<td>2 Refractive errors</td>
<td>7.7 6.4</td>
<td>68.1 39.8</td>
<td>121.9</td>
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<tr>
<td>3 Depression</td>
<td>15.8 0.5</td>
<td>77.6 4.8</td>
<td>98.7</td>
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<td>0.5 1.1</td>
<td>20.8 31.4</td>
<td>53.8</td>
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<tr>
<td>5 Unintentional injuries</td>
<td>2.8 1.1</td>
<td>35.4 5.7</td>
<td>45.0</td>
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<tr>
<td>6 Osteoarthritis</td>
<td>1.9 8.1</td>
<td>14.1 19.4</td>
<td>43.4</td>
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<tr>
<td>7 Alcohol dependence and problem use</td>
<td>7.3 0.4</td>
<td>31.0 1.8</td>
<td>40.5</td>
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<td>32.5 0.0</td>
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<td>9.0 15.1</td>
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<td>10 COPD</td>
<td>3.2 4.5</td>
<td>10.9 8.0</td>
<td>26.6</td>
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<td>11 Ischaemic heart disease</td>
<td>1.0 2.2</td>
<td>8.1 11.9</td>
<td>23.2</td>
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<td>12 Bipolar disorder</td>
<td>3.3 0.4</td>
<td>17.6 0.8</td>
<td>22.2</td>
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<td>13 Asthma</td>
<td>2.9 0.5</td>
<td>15.1 0.9</td>
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<td>14 Schizophrenia</td>
<td>2.2 0.4</td>
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<td>16 Alzheimer and other dementias</td>
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<td>1.3 7.0</td>
<td>14.9</td>
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<td>17 Panic disorder</td>
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<td>18 Cerebrovascular disease</td>
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<td>19 Rheumatoid arthritis</td>
<td>1.3 1.7</td>
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<tr>
<td>20 Drug dependence and problem use</td>
<td>3.7 0.1</td>
<td>8.0 0.1</td>
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COPD, chronic obstructive pulmonary disease.

Table I. Estimated prevalence of moderate and severe disability (millions) for leading disabling conditions by age, for high-income and low- and middle-income countries, 2004.

Table II. Leading global causes of Years Lost to Disability (YLD) in high-income and low- and middle-income countries, 2004.

<table>
<thead>
<tr>
<th>Low- and middle-income countries</th>
<th>YLD (millions)</th>
<th>Total YLD (%)</th>
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<tr>
<td>1 Unipolar depressive disorders</td>
<td>55.3</td>
<td>10.4</td>
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<tr>
<td>2 Refractive errors</td>
<td>25.0</td>
<td>4.7</td>
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<td>3 Hearing loss, adult onset</td>
<td>23.2</td>
<td>4.4</td>
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<td>4 Alcohol use disorders</td>
<td>18.4</td>
<td>3.5</td>
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<td>14.8</td>
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<tr>
<td>7 Birth asphyxia and birth trauma</td>
<td>12.9</td>
<td>2.4</td>
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<tr>
<td>8 Bipolar disorder</td>
<td>12.9</td>
<td>2.4</td>
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<tr>
<td>9 Osteoarthritis</td>
<td>12.8</td>
<td>2.4</td>
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<tr>
<td>10 Iron-deficiency anemia</td>
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COPD, chronic obstructive pulmonary disease.

The purpose of this review is thus to explore the risk of slow treatment response on the one hand, and the value of early changes in the treatment course on the other. Additionally, methodological reasons will be highlighted for the discrepancy between the delayed onset of antidepressant action hypothesis and the modern early improvement approach. Possible biologic mechanisms behind early improvement will be explored, and finally, current evidence regarding the ability of different antidepressant compounds to induce early symptom improvement will be summarized.

**Risks of slow response to antidepressant treatment**

True delayed onset of antidepressant efficacy has been connected with many primary depression-related risks, as patients remain symptomatic and functionally impaired during the initial treatment time, as well as in connection with secondary psychosocial issues. A prolonged time to alleviation of the acute illness burden not only prolongs the vocational disability, but also bears an increasing risk for chronicization of the current illness episode. This notion finds support in studies showing that the length of the current untreated episode of illness may be the strongest predictor of overall short-term and long-term outcome in major depression. The possible underlying pathophysiology for this, which has repeatedly been discussed in relation to several mental disorders, is a direct neurotoxic effect of the current depressive episode. Data in support of this notion come from a very recent high-resolution functional magnetic resonance imaging study on 20 medication-naïve patients with a first episode of major depression who were compared with 20 healthy controls and 20 subjects who had fully recovered after a first episode. Patients in an acute episode showed significant enlargement of both amygdalae, whereas there was no difference between healthy controls and recovered subjects. Furthermore, amygdala size correlated significantly with the depression severity.

Another major issue that seems to be connected with the slow response of antidepressant treatment is suicidality. In a study by Jick and coworkers, an increased risk of suicidal behavior was especially noticed during the first 9 days of treatment. The odds for suicidal behavior among patients first prescribed an antidepressant 1 to 9 days before their index date (ie, occurrence of suicidal ideation) were 4.07 (95% confidence interval [CI], 2.89-5.74) compared with patients who were first prescribed an antidepressant 90 days or more before their index date. This is in line with several studies on suicidal acts in inpatients and outpatients, showing the highest risk to be within the first week or month of commencement of antidepressant treatment. The early occurrence of suicidal ideation has constantly been connected with a mismatch between early symptom improvements like increased psychic and physical energy, and the more gradual resolution of depressed mood and hopelessness. One major confounder in this context is clearly the fact that there is a large overlap between predictors of poor treatment response and occurrence of suicidality. Persistent hopelessness during treatment might be one of the major psychopathological symptoms accounting for suicidal ideation during treatment, as shown by Maria Oquendo for unipolar and bipolar depressed subjects. The overlap between predictors of response and suicidality and the finding that suicidal acts occur soon after starting antidepressant treatment suggest that achieving a more rapid and enhanced treatment response, targeting core depressive symptoms including hopelessness, could help to substantially reduce the incidence.

A delayed onset in the effect of antidepressant treatment can also be associated with secondary psychosocial losses. It has been proven fairly well that depression limits quality of life, particularly through its impairment of the cognitive skills necessary for work, creating and maintaining relationships, being productive, and functioning in multiple domains. Beside from such issues, a prolonged time to antidepressant treatment response also increases the patient’s subjective experience of a lack of treatment efficacy, which may lead to frustration and damage to the patient doctor relationship, usually finally resulting in poor compliance rates. This latter issue is also reflected by the high dropout rates in placebo-controlled trials for nonresponding subjects.

**The unmet need for fast improvement in treating major depression: a new therapeutic paradigm?**

Early improvement and onset of antidepressant action has been a matter of research and discussion for decades. Nowadays, there is strong evidence pointing in the direction of true early antidepressant effects. Since delayed onset of antide-
pressant action bears considerable risks, would it not seem wise to further explore the potential role of early onset of antidepressant action as a surrogate end point for long-term sustained stability, given that at the same time it is associated with long-lasting benefits such as limitation of harmful neurobiological effects, limitation of poor outcome secondary to repeated depressive episodes, and limitation of enduring depressive symptoms? In a next step, specific therapeutic interventions leading to fast improvement could be developed.

But before the paradigm can be changed, one must think about the methodological problems and pitfalls that need to be considered in examining fast treatment response/effects. So far, the vast majority of data on the topic, presented in summary below, have relied on post hoc analysis or meta-analysis of large-scale placebo-controlled or naturalistic studies. There are almost no prospective trials in this field.

Data from randomized controlled trials showing drug placebo differences not earlier than week 3 or 4 usually rely on significant verum placebo differences in mean scores on a rating scale. But clearly, such an approach cannot detect early significant symptom changes in individuals, which clinicians regularly observe. An advantage would be the incorporation of responder and remitter analysis of such data, which would allow consideration of significant treatment benefits at the individual level. But we would still need to keep in mind that the current cut-off point for a response, ie, a 50% improvement from baseline, might be too strict to detect slight but significant early changes. Thus a growing body of literature suggests that a cut-off of a 20% improvement from baseline on a depression rating scale might be sensitive enough to detect early changes.14

Next, we should reconsider the instruments currently used as the gold standard in depression research. The Hamilton Rating Scale for Depression (HAM-D), for example, is well known to not be very sensitive at detecting treatment changes, as opposed to the Montgomery-Asberg Depression Rating Scale, which was specifically developed for this.15 But there are also other aspects of the study design that need to be taken into account. Most trials of antidepressants use weekly or biweekly measurements, which are too infrequent and wide-apart to detect early changes that can occur within hours or days. A very useful tool may be online life-charting, which is nowdays freely available on several Web sites (eg, www.moods wings.net.au).

One last aspect concerns statistical analysis of early improvement, which bears some unique features; in this area, patients have most often been investigated at different time points that depend on the individual. Statistical analysis should ideally rely on mixed models, including varied assessments as a random variable. In a direct comparison with placebo or an active comparator, it may be most sensitive and appropriate to use a survival analytic approach, although other methodologies can also provide useful information.16 Keeping all these limitations in mind, we will now briefly review the available evidence regarding the predictive ability of early response during antidepressant treatment.

How does early improvement predict later stable response and remission?
Traditionally it has long been thought that standard antidepressants take about 1 month for their antidepressant action to fully unfold, with a delayed onset of action of at least 2 weeks. Originally, Quitkin proposed in his pattern analytic approach that drug effects could not be observed before 3 weeks of treatment.17 An earlier improvement was supposed to be a placebo response, with a subsequent lack of sustained improvement, whereas the opposite was true for true drug responders who showed a delayed but sustained onset of response.17,18 More recently, this view has been questioned by a large number of authors who have not only emphasized that an earlier onset of response before 2 weeks is highly prevalent, but have also shown that it was highly predictive of lat-

![Figure](https://example.com/figure.png)


er outcome.19-21 An early improvement was thus defined as a 20% reduction in the initial HAM-D17 score within the first 2 weeks. Henkel and co-workers recently demonstrated in a large naturalistically treated sample of 1014 depressed inpatients that about 80% of all early improvers achieved full response at the final end point, whereas only 50% of the non-early improvers did so.14 Concerning remission, about 58% of all early improvers were also remitters at the final end point; by contrast, 63% of the non-improvers also became non-remitters at discharge (Figure).14 It appears that early improvement defined as a 20% reduction during the first 2 weeks.
may be an excellent trait variable for use in treatment decisions. As psychiatrists usually want to fully utilize the potential of each single drug and to minimize the risk of switching too early or changing a medication that might still start to work later on, the rate at which non-early improvers (corresponding to the sensitivity of early improvement as a predictor of later response) finally respond or remit might be the most clinically meaningful variable. In other words, if most non-early responders stay nonremitters or nonresponders, then further and earlier therapeutic interventions are indicated in order to improve the outcome.

In line with the data of Henkel et al, but even more striking, are very recent pooled data from a meta-analysis of randomized controlled phase 3 trials involving 6,562 patients carried out by the group of Armin Szegedi. The data showed that only 4% and 11% of the non-early improvers became stable remitters and responders, respectively, after 4 or more weeks. In other words, if a patient does not show at least some minimal improvement within the first 2 weeks, there is a 96% chance that they will also be a nonremitter after 4 or more weeks, and an 89% chance that they will be a nonresponder, if no changes are made to the medication regime. This leads to the conclusion that if after 2 weeks one can observe no improvement at all under a new antidepressant regimen, then the pharmacologic regimen should be adjusted or changed immediately rather than waiting for another 2 or 3 weeks. Before we go on deeper into the current knowledge of antidepressant compounds and their potential for inducing early symptom changes, we will briefly discuss the underlying biological mechanisms possibly involved in early treatment changes.

**Biologic mechanisms of early onset of antidepressant compounds**

Due to methodological difficulties, knowledge of the biology of antidepressant action is still very sparse. A very recent review by Marchedo-Vieira gives an excellent overview of this topic. Concerning the traditional view of a delayed onset, one of the most widespread theories is the two period model, initially proposed by Hyman and Nestler in 1996. In the first “initial phase,” there is a correction of presumably disturbed monoaminergic neurotransmission, which is followed by a second “adaptation phase,” during which there are enduring modulatory changes in critical cortical circuits related to long-term antidepressant response.

Today, a growing body of evidence supports the notion that mood disorders might develop from abnormalities in cellular neuronal plasticity cascades. The term “neuroplasticity,” which is regularly used in this context, refers to remodeling and development of new synapses and axonal and dendritic architecture, and the growth of new neurons. Amongst other neurotrophins and cytokines, one central factor that is involved in the regulation of neuroplasticity is brain-derived neurotrophic factor (BDNF). BDNF levels have also very constantly been associated with antidepressant response. In animal models, for example, bilateral infusion of BDNF in rodents has been shown to induce a fairly rapid antidepressant effect within 3 days after a single administration. This effect lasted for at least 10 days, which supports there being some degree of persistence.

More recently, glutamate has been found to be a central agent involved in the modulation of neuroplasticity. For example, Zarate and coworkers were able to show that a single i.v. dose of ketamine, an N-methyl-D-aspartic acid (NMDA) receptor antagonist, could induce a rapid and sustained antidepressant effect (within 110 minutes; over a period of 2 weeks) in subjects with treatment-resistant depression, compared with placebo. Of the 17 subjects investigated, 1 day after the i.v. dose, 71% met response criteria and 29% met remission criteria, and 35% remained responders for 1 week. Based on that observation, Machado-Vieira and coworkers hypothesized that this effect may be the result of two processes. The quick initial resolution of the depressive core symptoms might be more a result of an increase in glutamatergic throughput rather than a result of neuroplastic changes. Second, the sustained effect might be the result of early changes in neuroplasticity.

With regard to nonpharmacological interventions, sleep deprivation has also been proven to show early antidepressant action after the first night. Further developments like sleep deprivation combined with consecutive sleep phase advance, or combinations of sleep deprivation with lithium or antidepressant treatments, are known to produce sustained antidepressant effects. The rapid and early antidepressant effects of sleep deprivation have been ascribed to elevations in BDNF levels and changes in the glutamatergic throughput within the dorsolateral prefrontal cortex.

The next paragraph summarizes the current knowledge of antidepressant compounds so far to have demonstrated early symptomatic improvement.

**Onset of response in available antidepressants**

The demonstration of an early onset of response goes far back to the 80s, when Katz and coworkers began challenging the results of the landmark study of Quitkin showing that early improvement was associated with an assumed placebo response, as opposed to the later and sustained onset of antidepressant treatment action. Katz originally reported that an onset of action occurred within the first 10 days of treatment with tricyclic antidepressants. Unfortunately, this trial did not include a placebo control group. A little later, these shortcomings were overcome, and treatment-specific early changes were demonstrated in a study comparing desipramine and paroxetine with placebo. In this trial, significant early treatment effects occurred in the verum group, but not in the placebo group. Moreover, these effects were highly predictive of lat-time and depression treatment: the value of early treatment response – Möller and others
er response. Subsequently, Nierenberg demonstrated that more then 50% of patients ultimately responding to fluoxetine showed early symptom improvements after week 2. The very same group also showed that non-early improvement was highly predictive of poor 8-week outcome.19

In 2003, Szegedi and colleagues studied early improvement in a randomized controlled trial comparing mirtazapine and paroxetine in patients with major depressive episode. Early improvement as measured with a 20% reduction in the HAM-D total score was present as soon as week 2, and was highly predictive of later stable response and remission for both drugs. Less than 10% of patients not improving after week 2 became responders or remitters thereafter. Most recently, Szegedi replicated his findings in the previously described meta-analysis, using a dataset from randomized active or placebo-controlled trials of mirtazapine, in 6907 inpatients and outpatients. The classes of active comparators included a serotonin norepinephrine reuptake inhibitor (SNRI; venlafaxine), SSRIs (paroxetine, fluoxetine, citalopram, sertraline, and fluvoxamine), tricyclics (amitriptyline, doxepin, and clomipramine), as well as the tetracyclics maprotiline and trazodone. A total of 52% were taking mirtazapine. The majority of patients had at least a 20% reduction in the HAM-D17 total score by the end of week 2. Across all treatments, early improvement was a highly sensitive predictor of stable response (81%-98%) and stable remission (87%-100%), although specificity was limited (43%-60% and 30%-53% for response and remission, respectively).22

Three years earlier, a meta-analysis focusing on SSRIs revealed very similar results. A total of 50 randomized controlled trials on fluoxetine, fluvoxamine, citalopram, escitalopram, sertraline, and paroxetine including 5872 patients were analyzed.32 The main results revealed that treatment with SSRIs rather than with placebo was associated with clinical improvement by the end of week 1. In addition, the chance of achieving full response after week 1 (50% improvement on HAM-D) was significantly higher with an SSRI than placebo.

Most recent analyses of the first double-blind placebo-controlled trial on agomelatine including an active comparator (paroxetine) give additional support for an early onset of antidepressant action. The analysis for the time to first response indicated an initial significant effect (superiority over placebo) of agomelatine (paroxetine) give additional support for an early onset of antidepressant action. The analysis for the time to first response indicated an initial significant effect (superiority over placebo) of agomelatine (paroxetine) compared with placebo or one of seven different antidepressants. In the main, there was no indication of any delayed onset of antidepressant drug response. Instead the authors found a highly individual time pattern of recovery, along with continuous distributions of the time spent to the onset of improvement across all treatments and placebo. Effective antidepressant treatment appeared to trigger and maintain conditions necessary for recovery. Thus, affectively ill patients might be likely to possess a common "resilience-like mechanism" that largely controls recovery and that is inducible by sufficient antidepressant treatment.36

Conclusion

In summary, these findings may lead to the conclusion that careful following of the very early treatment course of depressed patients under antidepressant therapy can give extremely helpful and valuable information for improving individualization of treatment.

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An operational definition of time may involve describing a certain number of repetitions of one or another standard cyclical events. Time is a dimension tightly associated with the biology of living species; evolution has resulted in humans—as other organisms—adapting to repetitive temporal information from the 24-hour cycle determined by sunrise and sunset. This circadian rhythm reflects an approximate 24-hour cycle in the biochemical, physiological, and behavioral processes of living entities, which crucially influences human well-being and health. Increasing evidence from clinical and neurobiological research suggests that disrupted temporal organization impairs behavior, cognition, mood, sleep, and social activity, and may be implicated in mental disorders. It has been proposed that altered timing of the biological system, i.e., circadian malfunction, is a major core feature of mood disorders—in particular, depression. In depressed patients, circadian rhythms and homeostatic processes are disrupted, thereby affecting mood, sleep, activity, and a variety of biological functions such as hormone secretion and body temperature. Depression, therefore, appears to be a circadian rhythm disorder in which biological functions that follow rhythmic internally and externally generated time patterns are disturbed. This may be caused by individual genetic disposition, whereby an individual's socially-determined circadian profile is vulnerable to life events, that together with altered environmental time cues (zeitgebers), can destabilize the circadian homeostasis of the body and mind. Entrainment of circadian rhythms via internal pathways affecting the body's circadian clock, provision of regular external time cues, and normalization of homeostatic biological function promise acute and sustained symptom relief in depression and may prevent relapse over the long term.

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Time and Its Relation to the Circadian Rhythm

Time constitutes a component of the measuring system used to sequence events and to compare the durations of events and the intervals between them. Operational definitions of units of time, in which one states that a certain specified number of repetitions of one or another standard cyclical event constitutes a defined time unit, have helped significantly in improving our understanding and shaping modern theories regarding human pathophysiology, including theories relating to psychiatric disorders. Periodic events and periodic motion have long served as standards for units of time, including the most prominent daily recurring event, the apparent motion of the sun across the sky.
Humankind has developed in an environment that is exposed to the rotation of the earth around its own axis, which results in daily rhythmic changes in light intensity. As a consequence, over the course of evolution, organisms have developed cellular clock mechanisms sensitive to light, and have adapted by organizing their activities into 24-hour cycles determined by sunrise and sunset. This circadian rhythm reflects a roughly 24-hour cycle in the biochemical, physiological, and behavioral processes of living entities, with the term *circadian*, coined by one of the founders of modern chronobiology, the scientist Franz Halberg, coming from the Latin *circa*, “around” and *diem* or *dies*, “day,” meaning literally “approximately 1 day.” These circadian cycles do not simply reflect an organism’s passive response to environmental changes, such as the light-dark cycle, but rather represent pre-adapted endogenous rhythms, which arise from a timekeeping system within the organism and persist in the absence of environmental stimuli.1

Biological clocks exhibiting circadian rhythms exist in virtually all tissues, with a series of clock genes generating the rhythm through protein feedback effects on their own synthesis.2 It has been widely demonstrated that these multiple endogenous clocks are distributed in every cell of the organism,3 which may result in each organ having its own timed circadian rhythm. They represent self-sustained oscillator circuits, mediating the periodic induction of specific target genes, which are minimal genetic timekeeping devices found in the organism and persist in the absence of environmental stimuli.4 As a result, nearly all physiological and behavioral functions in humans follow distinct time patterns.

The most prominent circadian pattern in human behavior is the sleep-wake cycle, for which clock genes affect both circadian and homeostatic function.5,6 An endless list of human physiological and behavioral functions has been documented as being influenced by the confounding impact of circadian and homeostatic patterns. They range from mental and physical performance, to metabolism and energy homeostasis in the liver and intestine,7 to parameters of the cardio-metabolic system.8 Even memory formation and consolidation represent processes that are notably shaped by endogenous circadian oscillators.9 Recent studies also suggest that circadian rhythms play a role in sports performance.10

Among the most well-known rhythmic biological functions are the secretion patterns of hormones such as cortisol and corticotrophin, prolactin, growth hormone, and melanotonin, all of them being critically involved in the organization of human psychological function. Robust circadian rhythms are also found in core body temperature variation, urine output, and bronchial smooth muscle reactivity. These rhythms enable the organism to synchronize endogenous processes of the internal milieu and to anticipate the periodic fluctuations in its external environment, with the aim of optimally dealing with them.1

A hallmark publication in the early 2000s showed individual cellular clocks to be integrated into a stable and robust pacemaker with a periodicity of about 24 hours.11 This publication confirmed in mammals that circadian rhythms are synchronized by a central clock or pacemaker located in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus. This clock generates a genetically programmed endogenous rhythmicity, which is slightly longer than 24 hours and needs to be synchronized (*entrained*) to the 24-hour day by external timekeeping cues.12 These external cues have been named zeitgebers (coming from the German words, *zeit*, “time” and *geber*, meaning “giving”) and represent a variety of physical events (eg, change between daylight and darkness) and social events (eg, mealtimes, social contact, etc). Healthy human life is thereby assured by a circadian biological system in which time-related patterns, meaning the temporal cyclical organization of recurring events, are synchronized. This comprises a harmonized interaction between diverse clock functions in peripheral tissues, the orchestrating function of the master clock in the central nervous system, the appropriate influence of external time cues acting as rhythm-stabilizing zeitgebers, and homeostatic components positively masking the circadian functions. The latter, eg, the increasing sleep drive resulting from increasing duration of sleep deprivation, have to be taken into account when investigating the role of circadian malfunction.

**Temporal alterations in biological functions that affect human behavior and health**

While the importance of human circadian rhythms has been known about for centuries, it has been widely neglected in modern society’s way of life. In fact, people living in Western industrialized countries increasingly neglect their biological circadian disposition. Working around a 24-hour day, traveling across several time zones, internet-based intercontinental business, and access to 24-hour television are leading to an increasing number of people living their lives against their own biological clocks.13 The American National Sleep Foundation14 pointed out that between 1998 and 2005, the amount of Americans sleeping for less than 6 hours per night increased from 12% to 16%, while those sleeping for over 8 hours decreased from 35% to 26%. Obviously, we are marching toward a sleepless and chronopathological society.15

Increasing evidence suggests that disrupted temporal organization impairs behavior, cognition, affect, and emotion; furthermore, disruption of circadian clock genes impairs the sleep-wake cycle and social rhythms. Altogether, these alterations of physiological circadian function may be implicated in particular in mental disorders. This is supported by stud-
ies demonstrating interactions between circadian oscillators via molecular clocks, and the neural circuits subserving higher brain functions and behaviors crucially linked to mental health. In particular, disturbances in sleep and arousal, cognition, and mood show close relations to altered circadian rhythms. A variety of mental disorders have been related to disturbances in the temporal organization of biological functions, such as shift-work disorder, seasonal affective disorder, bipolar disorder including mania, major depression, nocturnal eating syndrome, schizophrenia, dementia, and others.

**Depression**

There are an increasing number of journal publications and books summarizing our present knowledge on the circadian basis of affective disorders. Among the evidence to come from neurobiological research supporting a dysregulation of the clock-related circadian system in depression, is the flattening and phase shift of the circadian profiles of core body temperature and of cortisol, prolactin, growth hormone, and melatonin secretion seen in depression. For more than two decades, evidence has been continuously increasing to suggest that a blunted amplitude of the circadian profile is the main chronobiological abnormality in depression. Elevated core body temperature with a diminished amplitude is the most consistently observed circadian abnormality in depression, and generally normalizes with clinical improvement.

Although not confirmed by all studies, a phase advance in the overall 24-hour pattern of body temperature has also been reported in many patients. As body temperature may be the most robust parameter indicating the output of the circadian pacemaker, changes to normal body temperature variation mirror a functional disturbance located at the central nervous level of circadian organization.

Plenty of evidence has been gathered to indicate a dysregulation of the hypothalamic pituitary adrenal axis in depression and an overall increase in cortisol secretion, with the largest effect at the nadir of the circadian rhythm, and an earlier onset of the first cortisol secretory episode, consistent with a phase advance of the cortisol circadian rhythm. Studies have also reported reduced melatonin secretion and a trend toward a phase advance of the melatonin circadian rhythm in patients suffering from major depression. Melatonin is secreted by the pineal gland, with major input from the SCN, thereby indicating a function of the central pacemaker in its secretion.

A most prominent finding in depression is alteration of the sleep-wake cycle, including sleep architecture abnormalities such as frequent awakenings, loss of slow-wave–rich deep sleep, and a shift of the position during the night of rapid eye movement sleep. These disturbances of the sleep-wake cycle are the most obvious circadian rhythm alteration in humans, resulting in the prominence of sleep disturbance as a feature of depression. Finally, results from animal models of depression have supported the presence of circadian malfunction through the identification of polymorphisms in circadian genes such as CLOCK, BMAL1, TIM, PER, NPAS2, and others associated with mood disorders. While research linking clock genes and mood disorders is still in its early stages, it suggests a likely involvement of these genes in the susceptibility to mood disorders.

Scientific debate has addressed several theoretical ways in which disrupted circadian rhythms might lead to depression. On the one hand, alterations in biological clocks at the molecular level could lead to neurobiological dysfunction, which in turn may lead to the depressive state. On the other hand, a primary circadian disturbance of the sleep-wake cycle could lead to insomnia that might facilitate or exacerbate the depressed state. Moreover, unpredictable changes to an individual’s circadian profile induced by chronic stress, life events, or physical disease may alter the stability of the circadian system. Changes in external time cues acting as zeitgebers may in addition further destabilize the thereby altered circadian system. As a result, desynchronization of the rhythmic features of biological and psychological function may cause the mental disease.

From the present evidence, one can conclude that the widely accepted biopsychosocial model of the pathophysiology of mental illness may be extended to include the important component of circadian rhythm alterations. Depression, therefore, appears to be a circadian rhythm disorder in which biological functions following rhythmic internally and externally generated time patterns are disturbed. This may be due to individual genetic disposition and a socially-determined circadian profile that is particularly vulnerable to life events, which, together with changes in environmental time cues, destabilizes the circadian homeostasis of body and mind (Figure 1).

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**Figure 1.** The circadian model of depression. The circadian rhythm is a self-sustained oscillation in gene expression that is driven by molecular clocks at the molecular level. The circadian rhythm is synchronized by environmental signals such as light, temperature, and social interactions. Disturbances in the circadian rhythm can lead to disruptions in sleep-wake cycles, mood, and other biological rhythms. The circadian rhythm is also linked to many diseases, including depression. The figure illustrates how disruptions in the circadian rhythm can contribute to the development and maintenance of depression.

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**Data Source:**

Clinical signs of circadian dysregulation in depression

The clinical finding that depression-related symptoms include sleep-wake disorder with nocturnal insomnia and daytime sleepiness, lack of activity, loss of appetite, and diurnal changes of mood has encouraged the idea that abnormalities in circadian rhythms may underlie the development of affective disorders. From the point of view of clinical psychiatrists, quite a number of depressive symptoms have a temporal pattern that parallels the circadian malfunction found in the biological parameters (Figure 2). Beside symptoms of a disturbed sleep-wake cycle, diurnal variation in depressive symptoms appears to be central to the core of depression. Yet, longitudinal investigation of individual temporal pattern, regularity, and relation to clinical state and clinical improvement has revealed little homogeneity. Morning lows, afternoon slump, evening worsening can all occur during a single depressive episode. Mood variability, or the propensity to produce mood swings, appears to be the characteristic that most predicts the capacity to respond to treatment.40

Circadian functions as targets in the treatment of mood disorders

The corresponding clinical and neurobiological findings in depression have stimulated the idea that the restoration of normal circadian rhythms could have antidepressant potential. It is well established that chronotherapeutics—behavioral and biological treatments based on the principle of circadian rhythm reorganization—contribute significantly to the treatment of affective disorders. These clinical interventions include sleep deprivation, shifting of sleep time (sleep phase advance), light and dark therapy, as well as circadian behavioral entrainment strategies (eg, social rhythm therapy). In contrast to pharmacological treatments, some chronobiological interventions such as sleep deprivation treatment dramatically reduce depressive symptoms within 24-48 hours in 40%-60% of depressed subjects.36 The aim of chronotherapeutic interventions, thought to act by shifting and resetting the circadian clock, is to normalize circadian disturbances in depression. A growing number of clinical studies support the usefulness of chronotherapeutic interventions, even as first-line treatment. Consensus has not yet been achieved in terms of defining the underlying chronobiological mechanisms of optimal methods of producing rapid and sustained antidepressant responses to circadian interventions.36 The therapeutic effects of such interventions are rapid and often transient, but they can be stabilized by combining them with other such interventions, or by combining them with common drug treatments41,42 (Table) or biophysical treatments like repetitive transcranial magnetic stimulation.43

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Intervention</th>
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<tbody>
<tr>
<td>Wake therapy</td>
<td>Partial or complete sleep deprivation</td>
</tr>
<tr>
<td>Phase advance treatment</td>
<td>Stepwise shift forward of the sleep-wake cycle (earlier to bed, earlier to rise)</td>
</tr>
<tr>
<td>Combined wake and phase advance treatment</td>
<td>Sleep deprivation followed by shift forward of the sleep-wake cycle</td>
</tr>
<tr>
<td>Light therapy</td>
<td>Application of bright white light</td>
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<tr>
<td>Combined light therapy and drugs</td>
<td>Add-on of bright white light to pharmacological treatment with antidepressants</td>
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<tr>
<td>Combined sleep deprivation and drugs</td>
<td>Add-on of partial or complete pharmacological treatment with antidepressants</td>
</tr>
<tr>
<td>Combined chronotherapeutics and drugs</td>
<td>Sleep deprivation, light therapy, and phase advance, plus antidepressants</td>
</tr>
<tr>
<td>Dark or rest therapy</td>
<td>Exposure to relaxed darkness in bipolar mania and rapid cycling patients</td>
</tr>
<tr>
<td>Mood stabilizers (lithium)</td>
<td>Dosed according to standards</td>
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<tr>
<td>Selective serotonin reuptake inhibitor (fluoxetine) and tricyclic antidepressants</td>
<td>Dosed according to standards</td>
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<tr>
<td>MT1 and MT2 melatonergic agonist and 5-HT2A antagonist (agomelatine)</td>
<td>Dosed according to standards</td>
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Table. Interventions with scientific evidence showing an effect on circadian function in depression. Based on data from references 41 and 42.
At a behavioral level, in clinical practice, it is necessary to re- set and to stabilize the circadian rhythm regulated by central and peripheral clocks, which have to be entrained through environmental and social cues. This demands appropriate en- trainment to the light-dark and sleep-wake cycles, as well as the provision of a sufficient level of social zeitgebers, including regular interpersonal contact, timed activities, and regu- lar meal times.

There is a growing body of evidence from recent research that even certain antidepressant drugs may have chronobi- ologic properties in the treatment of depression. This is the case in particular for drugs that may act at receptors located in the SCN, the human master clock. Lithium has been shown to change circadian periods and the phase position of circadian rhythms, and to enhance and prolong the therapeutic effect of sleep deprivation, ensuring the most likelihood of clinical benefit in patients with bipolar disorder, who demonstrate altered circadian rhythms. Lithium also slows down the ab- normally rapid circadian periodicities in patients with bipolar disorder, an effect that appears to be crucial to therapeutic success. There is converging evidence that the chronobi- ological effects of lithium on circadian cycles are essential for its therapeutic efficacy.

In the treatment of depression, tricyclic antidepressants as well as selective serotonin reuptake inhibitors such as fluox- etine have demonstrated some chronobiological effects in changing the circadian amplitude of body temperature and melatonin secretion and producing a phase advance in cir- cadian activity. Recently, the antidepressant agomelatine, an agonist at melatonergic MT1 and MT2 receptors and an antagon- istic at 5-HT2C receptors, has been proven to have robust clin- ical efficacy and tolerability in major depressive disorder. This drug binds to MT1, MT2, and 5-HT2C receptors, and ex- hibits marked circadian properties. Behavioral studies in animal models of depression demonstrated that agomelatine is able to dose-dependently alter circadian rhythms and to resynchronize the sleep-wake cycle in models with disrupt- ed circadian rhythms. In humans, it was shown to shift the circadian rhythm of melatonin secretion and the core body temperature in healthy individuals, and to restore the sleep architecture and sleep patterns of depressed patients.

Conclusion
In summary, the organization of psychobiological time patterns has a serious influence on human functioning. Resynchro- nization, normalization, and stabilization of circadian rhythms represent promising new pathways in the search for effective nonpharmacological and pharmacological treatments of depression. Strong and adequate entrainment of biological rhythms appears to be the key to good behavioral, cognitive, and emotional wellbeing. Resetting the internal clock in depression by considering the individual disturbed time pat- tern in a patient appears to be a promising therapeutic ap- proach that reaches even beyond the realm of psychiatry.

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Dépression et temps : quand l’horloge interne ne fonctionne pas

La notion de temps peut se définir comme la répétition d’événements cycliques standard, dimension étroitement associée à la biologie des espèces vivantes. L’évolution a conduit les humains – à l’instar des autres organismes – à s’adapter à des informations temporelles répétitives ajustées sur un cycle de 24 h déterminé par l’alternance jour/nuit. Ce rythme circadien se calque sur un cycle d’environ 24 h dirigeant les activités biochimiques, physiologiques et comportementales du monde vivant, et influant de façon décisive sur la santé et le bien-être humains. De plus en plus de données de la recherche clinique et neurobiologique tendent à montrer qu’une organisation temporelle perturbée déstabilise le comportement, la cognition, l’humeur, le sommeil et l’activité sociale, et qu’elle peut être impliquée dans les troubles mentaux. Il semble que la perturbation des mécanismes biologiques liés au temps – en d’autres termes un dysfonctionnement circadien – joue un rôle absoiument central dans le développement des troubles de l’humeur, en particulier de la dépression. Chez les patients déprimés, les rythmes circadiens et les processus homéostatiques sont perturbés, ce qui a pour conséquence d’affecter l’humeur, le sommeil, l’activité et différentes fonctions biologiques comme la sécrétion hormonale et la température corporelle. La dépression semble donc être un trouble du rythme circadien dans lequel les fonctions biologiques qui suivent des schémas temporels rythmiques gérés de façon interne et externe sont perturbées. Une prédistribution génétique individuelle peut en être la cause, le profil circadien individuel déterminé socialement devenant vulnérable à certains événements de vie. Cette prédistribution, associée à une altération des synchroniseurs environnementaux (zeitgebers), peut déstabiliser l’homéostasie circadienne physique et psychique. Le soulagement rapide et prolongé des symptômes dépressifs, mais également sans doute la prévention des rechutes à long terme, passe ainsi par l’entraînement des rythmes circadiens par l’intermédiaire des voies internes influant sur l’horloge circadienne corporelle, l’apport de synchroniseurs externes réguliers et la normalisation de la fonction biologique homéostatique.

Keywords: circadian rhythm; endogenous clock; sleep-wake cycle; physiology; behavior; homeostasis; external time cue; disruption; depression
Most biological functions are expressed in an oscillating manner within a 24-hour circadian period, regulated by endogenous biological clocks. The rhythms are generated in the suprachiasmatic nuclei, groups of neurons in the anteroventral hypothalamus, and are synchronized by regularly recurring environmental stimuli or “zeitgebers” (light, social stimuli, physical activity, etc). The different stimuli are conveyed to the suprachiasmatic nuclei through afferent pathways that utilize different neurochemical and neuroendocrine signals, such as glutamate, serotonin, and melatonin. In turn, the suprachiasmatic nuclei communicate with other brain regions and peripheral systems to impart or entrain circadian rhythms in behavioral and physiological processes. It is now known that other brain regions (ie, the hypothalamic nuclei, hippocampus, frontal cortex, etc) contain autonomous oscillators and are capable of generating circadian rhythms. From a molecular point of view, circadian clock mechanisms comprise a core set of genes whose expression oscillates in an autonomous manner generated by a transcription-translation negative feedback loop with a crucial delay between stimulus and response. Posttranslational modifications (ie, phosphorylation events) play a key role in this feedback loop. Recent evidence demonstrates that circadian autonomous oscillations are also evident in components of signaling cascades with a key role in memory formation, neuroplasticity, and depression; for instance, the mitogen activated protein kinases, brain-derived neurotrophic factor, and cAMP response element binding protein. This is thus opening up new lines of research in the field of psychiatry.

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Circadian rhythms in the brain: the role of the suprachiasmatic nuclei

Time-linked modifications are identifiable at all levels of biological functioning, from biochemical processes to whole organism behavior, and these changes are regulated by a system of endogenous regulatory biological clocks. Biological activities follow cycles of various lengths, from very short rhythms (ultradian) to rhythms with a period of nearly 24 hours (circadian), and rhythms with longer cycles, from a week, to a season, or even longer. Most biological functions are expressed in an oscillating manner within a 24-hour period: the rest/activity cycle and sleep phases, body temperature, blood pressure and heart rate, hormone concentrations in the blood (melatonin, cortisol, thyroid-stimulating hormone, insulin, growth hormone, and other hormones), hepatic metabolism and detoxification (cytochrome P450 en-
Connections of the suprachiasmatic nuclei (SCN) within the brain: rhythms of intercellular and intracellular processes – In search of lost time

The suprachiasmatic nuclei (SCN) are an approximately 10 000 neuron group in the anteroventral hypothalamus, where circadian rhythm generation is located. These neurons are bilaterally paired groups of neurons, containing approximately 10 000 neurons each, in the anteroventral hypothalamus situated just above the optic chiasm. Destruction of the SCN, either experimentally in laboratory animals or as a result of disease in humans, disrupts the ability to express any circadian rhythm. On the other hand, individual neurons from the SCN, when dissociated and held in vitro, retain a robust circadian rhythm in electrical firing that can be recorded for several weeks.

The rhythms generated by the SCN are synchronized to a daily pattern by regularly recurring environmental stimuli or “zeitgebers.” In usual environmental conditions, circadian biological clocks are reset daily to 24-hour astronomical time by the day/night cycle, ie, through the influence of light, the main zeitgeber. Other environmental factors that can serve as zeitgebers are the availability of food, social schedules, and social exchanges.

Light stimuli arriving at the nonvisual photo-receptive retinal ganglion cells are transmitted directly to the SCN by way of the retinohypothalamic tract (Figure 1), in which the putative neurotransmitter is glutamate. Another pathway that indirectly conveys light stimuli to the SCN is the geniculohypothalamic tract. This pathway, in which the principal neurotransmitters are γ-aminobutyric acid and neuropeptide Y, runs from the intergeniculate leaflet of the lateral geniculate complex. Moreover, the serotoninergic pathway from the raphe nuclei acts as a synchronizer of the SCN (Figure 1). Indeed, the SCN is one of the important target areas of serotonergic projections. Serotonin (5-HT) is the principal neurotransmitter in the retina-raphé input pathway to the SCN. The serotonergic system in the SCN is involved in the mechanism of entrainment and rhythm modulation through its receptors, which respond to photic and nonphotic stimuli, and it thus plays a key role in circadian clock resetting.

Binding studies have demonstrated the presence of different 5-HT receptors (5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2C}, and 5-HT_{7}) in the SCN with variable levels of expression. In particular, a high concentration of 5-HT_{2C} receptors has been reported. In situ hybridization investigations in rats have reported that transcription of 5-HT_{2C} messenger RNA is highest early in the morning, suggesting that 5-HT_{2C} receptors also have a circadian rhythm of expression.

In recent studies, it was shown that 5-HT_{1A} receptors, possibly with co-activation of 5-HT receptors, are implicated in the nonphotic effects on the main clock. By contrast, 5-HT_{1A} and 5-HT_{2C} receptors are involved in photic-like effects and, for the 5-HT_{2C} subtype only, in potentiation of photic resetting.

The timing of external zeitgeber stimuli can phase-shift the SCN, and this can have an important impact on circadian rhythms. For instance, light during the early part of the night causes a phase delay in the SCN, while light in the early morning causes a phase advance. Other zeitgebers, such as social activity and work schedules, can also either directly or indirectly affect the SCN, as they influence the timing of food intake, physical exercise, light exposure, and sleep. In the absence of external zeitgebers, individuals express their endogenous period of circadian rhythms. This period is generally different from the 24-hour period, and is called the free-running period. Conditions without zeitgebers are, for example, constant darkness or constant light, in comparison with the usual light and darkness alternation, and a common example of the occurrence of this is in blind subjects. The free-running inherent rhythm of the SCN is slightly longer than 24 hours.

**Selected abbreviations and acronyms**

- **BDNF**: brain-derived neurotrophic factor
- **CREB**: cAMP response element binding (protein)
- **MAPK**: mitogen activated protein kinase
- **NMDA**: N-methyl-D-aspartic acid
- **SCN**: suprachiasmatic nuclei

**Figure 1. Connections of the suprachiasmatic nuclei (SCN) within the brain.** PVT, paraventricular thalamic nucleus.

The main known afferent and efferent pathways from the SCN to various brain regions are shown schematically.
Environmental changes. Indeed, it was gradually discovered that the SCN communicates with other brain regions to impart or entrain circadian rhythmicity in physiological and behavioral processes. For example, sleep/wake cycles are modulated by an efferent pathway via the paraventricular nucleus of the hypothalamus, and via a multisynaptic pathway to the pineal gland where melatonin is synthesized at night and suppressed by light during the day (Figure 1). Melatonin, secreted by the pineal gland, transmits information about the occurrence and duration of darkness; during short winter days, the duration of nocturnal melatonin secretion increases, whereas it decreases during long summer days. Moreover, melatonin itself has a zeitgeber function; in fact, melatonin, secreted under the hierarchical dependence of the SCN, influences the SCN in return by acting through specific receptors in this area (Figure 1). Indeed, preclinical studies have demonstrated that with respect to other areas in the brain, the SCN have a particularly high concentration of melatonergic MT₁ and MT₂ receptors, which are temporally expressed in a circadian manner. It has been shown that expression of the MT₁ receptor is regulated by both light and the central pacemaker, with a peak level of gene transcription occurring during the middle of the night. A major development in research in recent years has been the discovery that beside the SCN, various other circadian clocks are present in organisms. We now know that various non-neuronal tissues and non-SCN brain regions (eg, hypothalamic nuclei, forebrain, olfactory bulb, pineal gland, and the cortex) contain autonomous oscillators and are capable of generating circadian rhythms when isolated from the organism and cultured in vitro (Figure 1). These peripheral oscillators (as opposed to the central SCN clock) rely on feedback loops composed of clock genes and proteins, just as in the SCN clock. In all tissues studied to date, 5%-10% of the transcriptome displays circadian rhythms (ie, up to 10% of the genes are clock-controlled genes), but the subset of rhythmic transcripts is almost entirely distinct among tissues. This implies that the role of the clocks found in the SCN and those in the different peripheral tissues is distinct, and must reflect the particular functions of each tissue. The diversity of secondary clocks in the brain, their specific sensitivities to time-giving cues, as well as their differential coupling to the master SCN clock, may allow more plasticity in the ability of the circadian timing system to integrate a wide range of temporal information. Furthermore, this raises the possibility that pathophysiological alterations of internal timing that are deleterious for health may result from internal desynchronization within the network of cerebral clocks. Interestingly, a novel SCN output pathway to the ventral tegmental area via the median preoptic nucleus has been recently described (Figure 1). This projection may function as the circadian regulator of behavioral processes such as arousal and motivation, further linking well-known behavioral observations to reward-related actions and circadian rhythmicity. Another example of a circadian regulator is the hippocampus, pivotal in neuronal plasticity, learning, and memory processes, which shows rhythmic gene expression relatively independent of the SCN. In this context, it has been recently demonstrated that clock-related genes are highly expressed in hippocampal pyramidal cell layers, and that the expression of both protein and mRNA varies with a circadian rhythm, independent from that of the SCN, since it is detectable in isolated hippocampal slices maintained in culture. This can allow for the initiation of intrinsic rhythms necessary for time-of-day-dependent memory formation, which can be—and probably need to be—desynchronized from the SCN rhythm.

Intracellular clock mechanisms

At the molecular level, circadian clocks use clock genes to generate self-sustained rhythmicity. Clock genes are expressed not only in the SCN, but also in extra-SCN brain regions as in most peripheral tissues. At their core, the clocks contain a cell autonomous oscillator that is generated by a transcription-translation negative feedback loop with a crucial delay between stimulus and response. In mammals, the circadian clock mechanism comprises a core set of genes that is highly conserved among species: Circadian Locomotor Output Cycles Kaput (CLOCK) and its paralogue neuronal PAS domain protein 2 (NPAS2), Bmal1 (also known as aryl hydrocarbon receptor nuclear translocator-like; Arntl), period homologue 1 (Per1), Per2, Cryptochrome 1 (Cry1) and Cry2 (Figure 2). During the day, the basic helix-loop-helix PAS-domain containing transcription factor Clock (or NPAS2) interacts with Bmal1 to activate transcription of a large number of output genes. Clock and Bmal1 also activate the transcription of the Per and Cry genes via E-Box sequences in their promoter, resulting in high levels of these transcripts (Figure 2).

The resulting Per and Cry proteins heterodimerize, translocate to the nucleus, and interact with the Clock–Bmal1 complex to inhibit their own transcription. The Cry proteins impair phosphorylation of Clock/Bmal1, thus reducing transcriptional activity of the dimer. During the night, the Per–Cry repressor complex is degraded; this leads to a reduction in the inhibitory complex through turnover, and the cycle starts again with a new round of Clock/Bmal1–activated transcription (Figure 2). Selectively in forebrain regions, NPAS2, a protein very similar to Clock, can bind Bmal1 and induce Per and Cry gene expression. NPAS2 may also function in the place of Clock in the SCN if the Clock protein is genetically disrupted.

In addition to the primary loop, there is a second negative feedback loop involving nuclear orphan receptor genes, such as Rev-erba, Rev-erbb, Rora, and Rorβ, whose transcription is activated by Clock–Bmal1 dimers (Figure 2). The result is the production of Rev-erbs and Rors with negative and positive regulatory effects on Bmal1 transcription, respectively. This secondary loop does not seem to be essential, but it is
Molecular mechanism of the core mammalian circadian clock.

In the nucleus, the Clock/Bmal1 dimer binds to a specific chromosomal site (E-box) thus activating the transcription–translation negative-feedback loop with a delay between transcription and the negative feedback. The figure depicts a simplified scheme of the mammalian circadian rhythms core clock that is a transcriptional-translational negative-feedback loop with a delay between transcription and the negative feedback. The Per1, Per2, Cry1, and Cry2 are turned on permanently, expression of Per1, Per2, Cry1, and Cry2 is rhythmic, being highest in the first part of the day. Light acts through the retina and direct neural pathways to the SCN to stimulate this feedback loop. Light acts through the retina and direct neural pathways to the SCN to stimulate this feedback loop. Light transmission to the retina results in membrane depolarization and an influx of Ca2+. The resulting activation of GluN2 receptors, leads to activation of the N-methyl-D-aspartic acid (NMDA) and metabotropic glutamate (mGLU) receptors and PACAP, leads to activation of the N-methyl-D-aspartic acid (NMDA) and metabotropic glutamate (mGLU) receptors and PACAP, leads to activation of the N-methyl-D-aspartic acid (NMDA) and metabotropic glutamate (mGLU) receptors and PACAP, leads to activation of the N-methyl-D-aspartic acid (NMDA) and metabotropic glutamate (mGLU) receptors and PACAP, leads to activation of the N-methyl-D-aspartic acid (NMDA) and metabotropic glutamate (mGLU) receptors and PACAP, leads to activation of the N-methyl-D-aspartic acid (NMDA) and metabotropic glutamate (mGLU) receptors and PACAP, leads to activation of the N-methyl-D-aspartic acid (NMDA) and metabotropic glutamate (mGLU) receptors and PACAP, leads to activation of the N-methyl-D-aspartic acid (NMDA) and metabotropic glutamate (mGLU) receptors and PACAP, leads to activation of the N-methyl-D-aspartic acid (NMDA) and metabotropic glutamate (mGLU) receptors and PACAP, leads to activation of the N-methyl-D-aspartic acid (NMDA) and metabotropic glutamate (mGLU) receptors and PACAP, leads to activation of the N-methyl-D-aspartic acid (NMDA) and metabotropic glutamate (mGLU) receptors and PACAP, leads to activation of the N-methyl-D-aspartic acid (NMDA) and metabotropic glutamate (mGLU) receptors and PACAP, leads to activation of the N-methyl-D-aspartic acid (NMDA) and metabotropic glutamate (mGLU) receptors and PACAP, leads to activation of the N-methyl-D-aspartic acid (NMDA) and metabotropic glutamate (mGLU) receptors and PACAP, leads to activation of the N-methyl-D-aspartic acid (NMDA) and metabotropic glutamate (mGLU) receptors and PACAP, leads to activation of the N-methyl-D-aspartic acid (NMDA) and metabotropic glutamate (mGLU) receptors and PACAP, leads to activation of the N-methyl-D-aspartic acid (NMDA) and metabotropic glutamate (mGLU) receptors and PACAP, leads to activation of the N-methyl-D-aspartic acid (NMDA) and metabotropic glutamate (mGLU) receptors and PACAP, leads to activation of the N-methyl-D-aspartic acid (NMDA) and metabotropic glutamate (mGLU) receptors and PACAP, leads to activation of the N-methyl-D-aspartic acid (NMDA) and metabotropic glutamate (mGLU) receptors and PACAP, leads to activation of the N-methyl-D-aspartic acid (NMDA) and metabotropic glutamate (mGLU) receptors and PACAP, leads to activation of the N-methyl-D-aspartic acid (NMDA) and metabotropic glutamate (mGLU) receptors and PACAP, leads to activation of the N-methyl-D-aspartic acid (NMDA) and metabotropic glutamate (mGLU) receptors and PACAP, leads to activation of the N-methyl-D-aspartic acid (NMDA) and metabotropic glutamate (mGLU) receptors and PACAP, leads to activation of the N-methyl-D-aspartic acid (NMDA) and metabotropic glutamate (mGLU) receptors and PACAP, leads to activation of the N-methyl-D-aspartic acid (NMDA) and metabotropic glutamate (mGLU) receptors and PACAP, leads to activation of the N-methyl-D-aspartic acid (NMDA) and metabotropic glutamate (mGLU) receptors and PACAP, leads to activation of the N-methyl-D-aspartic acid (NMDA) and metabotropic glutamate (mGLU) receptors and PACAP, leads to activation of the N-methyl-D-aspartic acid (NMDA) and metabotropic glutamate (mGLU) receptors and PACAP, leads to activation of the N-methyl-D-aspartic acid (NMDA) and metabotropic glutamate (mGLU) receptors and PACAP, leads to activation of the N-methyl-D-aspartic acid (NMDA) and metabotropic glutamate (mGLU) receptors and PACAP, leads to activation of the N-methyl-D-aspartic acid (NMDA) and metabotropic glutamate (mGLU) receptors and PACAP, leads to activation of the N-methyl-D-aspartic acid (NMDA) and metabotropic glutamate (mGLU) receptors and PACAP, leads to activation of the N-methyl-D-aspartic acid (NMDA) and metabotropic glutamate (mGLU) receptors and PACAP, leads to activation of the N-methyl-D-aspartic acid (NMDA) and metabotropic glutamate (mGLU) receptors and PACAP, leads to activation of the N-methyl-D-aspartic acid (NMDA) and metabotropic glutamate (mGLU) receptors and PACAP, leads to activation of the N-methyl-D-aspartic acid (NMDA) and metabotropic glutamate (mGLU) receptors and PACAP, leads to activation of the N-...
As an example, several studies have pointed out a role for Erk-MAPK in the regulation of the circadian system in the SCN. Early studies showed that the MAPK cascade functions as one of the first transduction steps leading from light stimulation to rapid transcriptional activation, an essential event in the entrainment process. More recently, it was shown that MAPK is autonomously activated in the SCN, and that inhibition of MAPK activity results in dampened rhythms and reduced basal levels in circadian clock gene expression at the SCN single neuron level. Furthermore, MAPK inhibition attenuates autonomous circadian neuronal firing rhythms in the SCN, thus suggesting that light-independent MAPK activity contributes to the robustness of the SCN autonomous circadian system.

Temporal abundance and activity of Per are regulated by casein kinases Iα and Iε (CKIα/ε), which through phosphorylation, lead to modulation of degradation and cellular localization of the Per protein. Recent work demonstrated that circadian rhythms were completely disrupted by two different approaches targeting the kinase activity and specific interaction between the kinases and the substrate, thus indicating that CKIα/ε are essential for rhythm generation.

Biochemical studies revealed that GSK-3β phosphorylates Per2 for nuclear localization, Cry2 for proteasomal degradation, and Rev-Erbα for stabilization.

Recently, it was also shown that chromatin modifications through acetylation, deacetylation, and methylation of histones bound to promoter regions of core clock genes participate in the regulation of oscillating transcription. Moreover, it was reported that the Clock gene possesses intrinsic histone acetyltransferase activity, and that the activation of core clock genes by Bmal1/Clock heterodimers is indeed preferentially coupled to histone acetylation.

A role for brain-derived neurotrophic factor and related signaling in the regulation of circadian rhythms

Recent observations have suggested that circadian cycling of specific molecular signaling pathways may underlie these general cognitive phenomena. Brain-derived neurotrophic factor (BDNF) and its cognate receptor, the TrkB tyrosine kinase, are well-known mediators of synaptic plasticity in both developing and mature neurons. The neurotrophin BDNF has been implicated in the regulation of neuroplasticity, gene expression, and synaptic function in the adult brain, as well as in the pathophysiology of neuropsychiatric disorders and the mechanism of action of antidepressants. A growing body of evidence also supports a role for BDNF and TrkB in the modulation and mediation of circadian rhythms. As a starting point, high levels of expression of BDNF and TrkB were demonstrated in the rat SCN. It was reported that BDNF protein and mRNA levels in the rat SCN showed evident signs of variation over the course of a circadian cycle. The SCN content of BDNF protein remained low throughout the subjective day, began to rise early in the subjective night, and reached peak levels near the middle of the subjective night. BDNF mRNA levels in the SCN reached maximal values during the early subjective day, approximately 16 hours before the peak in protein content. After declining during the middle of the subjective day, the content of BDNF mRNA in the SCN remained at basal levels until the late subjective night. Diurnal variation in BDNF protein expression levels was demonstrated in the cerebellum, hippocampus, and cerebral cortex. In the same study, it was shown that CREB, a transcription factor regulating BDNF expression, was greatly activated by the phase advance in the entorhinal and visual cortex, suggesting the existence of CREB-mediated pathways of BDNF synthesis that are responsive to external light input.

Converging evidence supports the hypothesis that BDNF serves to gate photic phase shifts: (i) blocking TrkB receptors inhibits light- and glutamate-induced phase-shifts; (ii) light-induced phase shifts are substantially attenuated in BDNF+/- mice; and (iii) exogenous BDNF administration during the subjective day allows light and glutamate to induce phase-shifts in the daytime in vivo and in vitro, respectively.

More recently it was shown that as in the hippocampus, proteins from the plasminogen activation cascade responsible for BDNF activation are also present in the SCN, such as plasmin, plasminogen, tissue-type plasminogen activator, etc. The data support the hypothesis that these proteins regulate the conversion of proBDNF to mature BDNF (mBDNF) in the SCN, and that mBDNF availability acts as a gating mechanism for photic phase resetting. It is noteworthy that these proteins generally interact extracellularly, often bound to the extracellular matrix. As such, the consideration of processes that modulate SCN circadian clock phase-resetting should be expanded to include extracellular as well as intracellular mechanisms.

Interestingly, the presence of a diurnal BDNF rhythm was also recently demonstrated in humans: plasma BDNF in human healthy males displays highest concentrations in the morn-
ing, followed by a substantial decrease throughout the day, and the lowest values at midnight. Moreover, plasma BDNF levels were positively correlated with those of cortisol.45

Data from the same group recently showed the existence of a correlation between the daily levels of plasma BDNF and cortisol in women, corroborating the hypothesis of coregulation of cortisol, BDNF, and sex steroids in humans. This correlation suggests the possibility that glucocorticoid and neurotrophic tone may play a synergic role in the homeostasis of cerebral functions.46

It is known that one of the most common features of depressed patients is an altered hypothalamic-pituitary-adren- nal axis, with high glucocorticoid secretion. It is possible to hypothesize that variations in BDNF levels, such as those observed in psychiatric patients, may also be related to disturbances in the function of those structures involved in determining circadian rhythms either directly (SCN function), and/or indirectly (altered release of glucocorticoids that are modulated by glutamatergic innervation of the SCN).

It should be reminded that the transcription-regulating cAMP/ERK/CREB pathway, together with other signaling pathways, in particular the CaMKIV mediated signaling, is a major regulator of BDNF modulation in hippocampus, and has been suggested as having a role in both the pathophysiology of depression and the mechanism of action of antidepressants.38,47-49 During the last few years, it has been largely demonstrated that BDNF is involved in the mechanism of action of anti-depressant drugs; in particular, an increase in BDNF expression—both mRNA and protein—follows antidepressant administration in both experimental animals and human patients.39,49

Recognition that circadian rhythm disruption also plays a key role in mood disorders has led to the development of the new antidepressant agomelatine, which is endowed with a novel mechanism of action distinct from that of currently available antidepressants. Agomelatine is an agonist of the melatonergic MT1 and MT2 receptors, and an antagonist of 5-HT2C receptors. The antidepressant activity of agomelatine is proposed to stem from the synergy between these sets of receptors, which are key components of the circadian timing system. Recent data from various groups, including ours, showed that agomelatine led to an increase in BDNF expression in treated animals, and that this effect follows a specific temporal profile and is mediated by a functional interaction between the melatonergic MT1/MT2 receptors and the serotonergic 5-HT2C receptors.50

Conclusion
In conclusion, alteration of circadian timing plays a crucial role in mood disorders. Since intercellular and intracellular processes in the brain implicated in the pathophysiology of psychiatric diseases follow a circadian rhythm regulation, this phenomenon may have important implications in the development of new agents in psychiatry.
43. Michel S, Clark JP, Ding JM, Collwell CS. Brain-derived neurotrophic factor and neurotrophin receptors modulate glutamate-induced phase shifts of the suprachiasmatic nucleus. Eur J Neurosci. 2006;24:1109-1116.

Keywords: suprachiasmatic nucleus; circadian rhythm; clock gene; transcription factor; brain-derived neurotrophic factor; MAP kinase

CERVEAU ET TEMPS : RYTHMES DES PROCESSUS INTER- ET INTRACELLULAIRES

La plupart des fonctions biologiques s’expriment de façon oscillante sur un rythme circadien de 24 heures, régulé par une horloge biologique endogène. Les rythmes sont produits dans les neurones appartenant aux noyaux suprachiasmatisques (NSC), ensemble pair de noyaux de l’hypothalamus pérventriculaire, et sont synchronisés par des stimuli sociaux, activité physique, etc. Ces différents stimuli sont transportés jusqu’aux NSC par des voies afférentes chiasmatic nucleus. Ensemble pair de noyaux de l’hypothalamus pérventriculaire, et sont synchronisés par des stimuli sociaux, activité physique, etc. Ces différents stimuli sont transportés jusqu’aux NSC par des voies afférentes (par ex.; la phosphorylation) jouent un rôle clé dans ce rétrocontrôle. Des données récentes montrent que des oscillations circadiennes autonomes in-vivo interviennent à certains étages des cascades de signalisation ayant un rôle central dans la formation de la mémoire, la neuroplasticité et la dépression ; par exemple les MAP2K (mitogen activated protein kinases), le BDNF ou facteur neurotrophique (brain-derived neurotrophic factor) et le CREB (cAMP response element binding protein). Ces données ouvrent de nouvelles perspectives de recherche dans le domaine de la psychiatrie.


LE FACTEUR TEMPS DANS LE TRAITEMENT DE LA DEPRESSION : INTÉRÊT DE LA RÉPONSE PRÉCOCE AU TRAITEMENT

La dépression majeure reste encore une maladie dévastatrice, comme le reflètent les statistiques les plus récentes de l’Organisation Mondiale de la Santé, qui la désignent comme source principale d’années perdues pour cause d’in- capacité. L’adaptation du traitement psychopharmacologique à chaque patient individuel en est à ses débuts, malgré les avancées récentes. Cette individualisation pourrait bénéficier de l’utilisation de facteurs prédictifs tels la réponse précoce au traitement. Il existe aujourd’hui un vaste consensus au sein de la communauté scientifique sur les faits suivants : 1) les effets des traitements antidépresseurs se manifestent de façon précoce, dès les 2 premières semaines ; et 2) ces effets positifs sont d’une grande valeur pronostique. Ces données sont toutefois encore largement ignorées par la plupart des recommandations thérapeutiques concernant cette pathologie. Cet article fait le point sur les pièges méthodologiques dans l’évaluation de la précocité de la réponse au traitement, analyse les concepts actuels ayant trait à d’éventuels mécanismes biologiques impliqués dans cette réponse et récapitule les connaissances actuelles sur les caractéristiques des réponses précoce induites par les médicaments aujourd’hui disponibles. Cet article examine enfin les raisons qui alimentent encore la vieille croyance en l’apparition tardive de la réponse au traitement antidépresseur, et leurs répercussions sur le plan clinique.

Keywords: depression; early response; predictor; treatment effect; remission

Time and depression treatment: the value of early treatment response – Möller and others
THE QUESTION

In the treatment of depression, early improvement of the patient is clearly desirable, not least because it ensures better adherence with treatment. An increasing number of studies are looking at the issue of early symptom improvement and, importantly, the implications for achievement of response and remission. Does the early improvement of depressive symptoms with treatment predict antidepressant response? Are there certain symptoms that are particularly important in this respect?

**Is early improvement predictive of antidepressant response?**

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10. M. Wong, *Hong Kong*
11. R. M. Zaratiegui, *Argentina*
A fundamental issue in antidepressant therapy concerns predictors of therapeutic response. There is numerous evidence in the literature\(^1\) to\(^4\) showing that the delayed appearance of a therapeutic effect, in addition to increasing the risk of suicide, prolongs the individual’s and family’s suffering, while an early improvement increases positive outcomes and the compliance with treatment. Szegedi et al\(^1\) suggest that improvement in an individual in the early stage of treatment is a predictor of future response.

Previously, Segman et al\(^2\) and more recently, van Calker et al\(^3\) reported that early improvement predicts later response, remission, and resistance to treatment, because in their studies, those who didn’t show an early improvement (within the second week of treatment) had a low probability of achieving a delayed therapeutic response or remission. Some authors have stated that clinical improvement within the second week of treatment predicts, with high sensitivity, the responses in the 4th and 6th weeks.\(^4\) Similar results were obtained in a recent naturalistic prospective study conducted on a sample of 795 patients with major depression,\(^5\) in which it was shown that an improvement in the first 2 weeks of treatment predicted the rate of delayed response and remission, even in hospitalized patients with more serious disease.

According to researchers, a low or no initial response to treatment could justify an accelerated switch to alternative treatment. There are many variables that directly influence the latency time to clinical improvement. Several studies have shown population characteristics that may be identified as possible factors affecting the latency time to therapeutic response, such as the episode’s depression severity, the duration of the episode before the start of treatment, and the medical history of response to previous drug treatments.\(^6\) These aspects, together with the pharmacodynamic and pharmacokinetic characteristics of the drug, as well as characteristics of the individual patient, such as age, personality, and genetic variables (T and C variants of the 5-HT\(_{2A}\) receptor), contribute to modify the said latency time.

Other research has indicated some variables involved in a poor therapeutic response, such as low socioeconomic status and the presence of anxiety symptoms in the period preceding the start of treatment. These variables in elderly depressed patients are responsible for increased suicidal ideation. Another study identified six patient characteristics, in addition to depression severity, that are involved in the outcome of various antidepressant treatment types: social dysfunction, cognitive dysfunction, expectation of improvement, endogenous depression, double depression, and the duration of current episode.

Therefore, we must take into account all those factors that can increase the latency period and hence the disease time, thus avoiding the absence of remission, presence of residual symptoms, or resistance to treatment, because an early response to antidepressant therapy implies a better result for the entire duration of treatment, thus constituting a factor that is predictive of results in the medium and long term.

### References

In the treatment of depression, clinicians frequently need to carry out early identification of nonresponders and promptly implement an alternative treatment strategy deemed to be superior, rather than waiting 4-6 weeks on antidepressant treatment, as stated by the current guidelines. Such practice invariably serves to reduce suicide risk and unnecessary drug exposure during ineffective treatment, while increasing adherence and the chance of a better outcome.\(^1\)

Current guidelines are based on results indicating that the antidepressant effects within the first few weeks are in reality likely to be a placebo response of an abrupt and nonpersistent nature, dissimilar to a true drug effect.\(^2\)\(^,\)\(^3\) This evidence of a delayed response to antidepressants has been widely accepted in psychiatric practice and research fields. However, data regarding early onset of antidepressant action within the first 14 days of treatment have recently increased. In addition, an early therapeutic effect has been suggested to be the best predictor of response to antidepressant at end point\(^1\)\(^,\)\(^4\) and is also positively related to the restoration of psychosocial functioning.\(^5\) A recent large meta-analysis of 41 clinical trials including 6562 depressive patients, showed that early improvement at 2 weeks predicted response and stable remission, with high sensitivity of above 80%. In this meta-analysis, negative predictive values for stable response and remission were very high (82%-100%), but positive predictive value was relatively low (19%-60%).\(^7\)

When applying these data regarding early improvement as a response predictor in real clinical practice, it is necessary to consider the limitations of the data, as most studies were not specifically designed for such a purpose. In addition, thorough examination of factors such as the cut-off values for early improvement, later response, and remission, and the decision time point is necessary. The definitions of such factors were made somewhat arbitrarily, and are not suitable for real practice. Studies have not yet yielded any information regarding the long-term outcome (eg, recurrences) and the differences among many kinds of antidepressants (eg, selective serotonin reuptake inhibitors [SSRIs] vs serotonin norepinephrine reuptake inhibitors).

Now, I’d like to address the reported possibility of there being differential improvement patterns for several depressive symptoms.\(^6\) All symptoms of depression did not improve simultaneously. The order and degree of improvement in depressive symptomatology might result from different neurochemical actions among antidepressants. Certain symptoms may improve more quickly than others (eg, anxiety and depressive mood vs SSRIs vs serotonergic retardation with desipramine).\(^8\) In such cases, a symptom-specific measure may be more sensitive than measurement of global symptom severity for detecting early antidepressant effects.

It remains uncertain as to which type of symptom improvement would be more predictive of long-term outcome. The emotional domain (eg, depressive mood and anhedonia) has been regarded as the classical core of depression. Recently, however, anxiety, residual somatic symptoms, and cognitive dysfunction have increasingly received attention as treatment targets. Early improvement of anxiety might predict higher response and remission. Also, it is known that residual sleep disturbance and sexual dysfunction are significantly associated with subsequent relapse or recurrence and subsequent poor treatment outcome. The biological bases of these symptoms in depression were studied extensively in the last decade.

Despite many limitations and problems, in light of consistently high negative predictive values obtained in recent data, it would be advisable to alter the current treatment strategy in the case of insufficient improvement within a couple of weeks of standard antidepressant treatment. Prospective studies specifically designed to address this issue are needed in the future.

References

Is early improvement predictive of antidepressant response?
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A number of studies on efficiency predictors in the treatment of major depressive disorder have been based on the standardization of treatment efficiency evaluation, using remission (RM), response (RS), partial response (PR), and nonresponse (NR) criteria. In one study involving 130 patients, researchers studied “baseline” predictors (social and clinical characteristics at beginning of treatment) and “process” predictors (changes during the 8-week antidepressant treatment course, including time to initial response [IRS], ie, a reduction of at least 25% on the Hamilton Rating Scale for Depression [HAM-D]). Stratification of various drug treatment efficiency predictors showed IRS time to be the most important. A total of 24.6% of studied patients developed IRS during the first week of treatment. Of these, 68.8% were categorized as being in RM, and 31.2% as RS. Patients with longer IRS times less frequently achieved RM and RS and more frequently achieved PR. For patients who developed IRS during the 2nd treatment week, 46.2% achieved RM, 36.5% RS, and 6.9% PR. For patients with IRS in the 3rd treatment week, 28.6% achieved RM, 34.3% RS, and 37.1% PR. For patients with IRS in the 4th week, 2.3% achieved RS and 17.3% PR. For patients with IRS in the 5th week (26.9% of all patients), 33.3% achieved RS and 66.7% PR. Two patients developed IRS in the 6th or the 7th week. One of these achieved RS, the other PR. None of the nonresponders developed an IRS. This regularity was found to be independent of the antidepressant administered.

The period during which IRS develops is crucial, as it determines the efficiency of later treatment stages. However, this is a “silent” (latent) period regarding antidepressant effect. Results indicate the absence of a strong correlation between the development of IRS and the antidepressant action of the drug. At the same time, this period is remarkable for its most evident placebo effect. The role of this period in the prediction of antidepressant treatment efficiency was studied in 83 patients, who underwent 1 week of placebo treatment followed by 4 weeks of antidepressants. A total of 46.9% of all major depressive disorder patients (HAM-D, 22.8 ±3.7) became placebo responders during the first week of placebo treatment. By the end of antidepressant therapy, all of them entered the RS group (HAM-D score reduction of ≥50%). As for placebo-NR patients (53.1% of all participants), only 55% of them became responsive to antidepressant therapy. The results of this study indicate that response to placebo is a complex reaction of the whole human body, including multiple changes at the clinical, neurochemical, and neurophysiological levels. The monoamine excretion test revealed increased activity of the catecholamine neurotransmitter system in the placebo-responsive group (n=15) compared with placebo nonresponders (n=18), who did not develop the same changes (placebo responders: histamine background level 14.8 ±1.6 ng/min, placebo period 18.9 ±1 ng/min [P<0.01]; dopamine background level 112.6 ±2.3 ng/min, placebo period 124.8 ±2.6 ng/min). The same was true for the indolamine system (placebo responders: 5-OT background level 116.4 ±2.6 ng/min, placebo period 127.8 ±1.9 ng/min [P<0.05]).

Test results confirmed the neurophysiological basis of the placebo effect (narrow-band spectrum analysis of multichannel electroencephalogram was used). This effect features a marked single-type reaction of an increase in the low and medium-frequency range of α-rhythm (6.3-9.0 Hz and 9.0-10.2 Hz), in contrast with nontypical, feebly marked single bands (mostly of β1-rhythm) in placebo-NR (P<0.05). These data demonstrate higher neurophysiological reactivity in placebo-responsive patients. Further antidepressant therapy was found to lead to a completely different electroencephalogram profile (restoration of physiological asymmetry in low- and medium-frequency α-rhythm signals in central and frontal areas of the brain). These changes developed only in patients who were responsive to active therapy.

These data support the idea of the initial reactivity of neurobiological mechanisms to certain drugs in placebo-RS patients (which may be genetically determined). The manifestations in the early stages of therapy include sensitivity to placebo and to nonspecific actions of antidepressants. This may also be related to the neuroplasticity of certain cerebral structures (brain-derived neurotrophic factor hypothesis). IRS may be considered to be a specific independent predictor of RM achievement. The new major depressive disorder treatment strategy implies a personalized approach to the adjustment of the treatment regimen, dependent on a patient’s individual IRS time.
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Time to onset of action and time to response are of great clinical importance; however, they have rarely been included as an outcome variable in older depression studies. While there are patients who have an early response to antidepressant treatment, most antidepressant treatments suffer from limited efficacy and a slow onset of action. Slow, delayed onset of action and delayed response during antidepressive treatment—which has already been described in the classical textbooks—is a source of frustration for patients and their families, a major reason for nonadherence, and may contribute to suicidality.

The predictive value of early improvement and response or nonresponse has been investigated. Szegedi et al. published data suggesting that early improvement predicts later stable response and remission with high sensitivity. Improvement occurred in 65% of paroxetine-treated patients and 73% of mirtazapine-treated patients within 2 weeks. On the other hand, early nonresponse may predict poor later outcome: nonresponse to fluoxetine predicted the 8-week outcome as early as week 2. The results of a meta-analysis suggest that “true” antidepressant response can occur in the first 2 weeks as well as the first week of treatment of major depressive disorder. A recent naturalistic study on a large sample (n=795) of inpatients with major depression confirmed the findings of randomized controlled trials: early improvement in the first 2 weeks may predict later response and remission with high sensitivity, even in hospitalized patients suffering from a more severe degree of depression. Fewer side effects and early onset of action both contribute to an improved adherence to medication.

Thus it is important to develop antidepressant drugs that have an early onset of action. Drugs with a dual action demonstrated this benefit in several studies; for example, in two studies, a significantly greater proportion of patients treated with venlafaxine than placebo had a clinically meaningful drug response within the first 2 weeks of treatment, and this early response persisted for the duration of the studies. Different antidepressants may have different symptom profiles for early improvement/response; eg, desipramine treatment was found to be associated with early improvement in motor retardation and depressed mood, while anxiety and hostility symptoms showed early response to paroxetine. Agomelatine, an antidepressant with a new mode of action, has also been demonstrated to have an early onset of action, especially in the improvement of sleep, which is included in its Summary of Product Characteristics: “From the first week of treatment, onset of sleep and the quality of sleep were significantly improved without daytime clumsiness as assessed by patients.”

A study comparing agomelatine with venlafaxine and another study comparing agomelatine with sertraline demonstrated earlier and superior improvement in wake/sleep disorders associated with depression.

Time to response data help in deciding how long to continue with a drug treatment if it has not yet shown an onset of action. Time to response data also help in making some other treatment decisions, such as dose increases or augmentation of the current treatment with another drug or psychotherapy. Early onset of action may improve adherence, predict later response and remission with high sensitivity, and also reduce relapse rates even in hospitalized patients suffering from a more severe degree of depression. In conclusion, available data support the notion that early onset of therapeutic action in depression is related to greater efficacy of antidepressant treatments.

References
Several antidepressant drugs are commonly used for the treatment of this serious condition, depression, with one of the greatest pitfalls of currently-available antidepressants being their latency of therapeutic effect. Since most, if not all, of them usually require 3 to 4 weeks to achieve symptom relief, one is commonly faced with patients still experiencing symptoms, leading to functional impairment and increased suicide risk. Such latency of effect has been commonly linked to secondary psychosocial deficits.

One is faced with a clinical picture of urgent demand for prompt and efficacious treatment in order to restrict the latency time to achievement of therapeutic effect. Such an effect, despite patients taking an antidepressant for weeks, is not attained by a non-neglectable number of patients, who despite long-term antidepressant exposure, still fail to achieve remission. Roughly half of depressed patients fail to respond to the first prescribed antidepressant, while two thirds will fail to achieve remission. An absence of response within the first 2 weeks of antidepressant treatment may lead to a lower response probability at a later time frame. Thus, shortening the antidepressant latency, coupled with reducing both partial response and failure to achieve remission, becomes a quest in itself.

Data from controlled studies (post-hoc analyses), meta-analysis, and even large-scale observational studies in clinical settings have questioned the antidepressant latency length, suggesting that some current antidepressant treatments can exert some initial beneficial effects early, ranging from the first to the second week of the patient’s exposure. Although a number of methodological study limitations can be identified relating to insufficient measurement of early response and data arising from studies not specifically designed to assess speed of antidepressant action, the search for treatment efficacy predictors is utterly relevant and can be translated into an effort to identify factors involved in non or partial remission. Among these, depression severity, length of episode before treatment commenced, comorbid anxiety symptoms, comorbid disorders, and painful or physical symptoms like fatigue have been reported. With regard to the latter, if present at the onset of depression treatment, there is a lower chance of achieving remission.

So far, the most sensitive predictor of stable response and remission available is the decrease of depressive symptoms at an early stage of treatment. Such a predictor appears to be independent of the antidepressant (either monotherapy or combination), even when combined with psychotherapeutic approaches.

Nevertheless, one has to emphasize that a fast response to an antidepressant treatment might not be due to a specific effect of the treatment, and factors like the placebo effect (especially in sudden- and fast-onset improvement) or non-treatment-specific effects also have to be considered. Differentiation of pharmacological from placebo effects is reflected in the lack of sustained improvement in the short term.

Symptoms like depressed mood and psychomotor slowing, as well as physical symptoms such as pain, are the symptoms that through their improvement, appear to lead to remission. However, even if there is improvement in these symptoms, one should exert caution regarding residual symptoms of depression, which, if present, are predictors of future relapse and reduced psychosocial adjustment. The clinician should be aware of sleep disturbances, sexual dysfunction, fatigue, and excessive daytime sleepiness, which are the most common residual symptoms, and for which treatment should be adjusted from the very beginning.

Not yet at a clinical level, recent research has produced promising results with the use of frontal quantitative electroencephalography, which, combined with an antidepressant treatment response index, has been shown to be capable of predicting response as early as the first week with at least two antidepressants from different classes.

References


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Depressive disorders affect approximately 5% of the population each year, and are now the fourth leading cause of the global disease burden, and the leading cause of disability worldwide. Depression seriously reduces quality of life for individuals and their families, is a risk factor for suicide, and often worsens the outcome of other physical health problems. Current antidepressants usually require several weeks to produce beneficial clinical effects, and are only effective in achieving remission (minimal to no symptoms) in less than half of depressed patients after acute antidepressant treatment. The lessons from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, which used a 50% score reduction on the 17-item Hamilton Rating Scale for Depression (HAM-D) to define response, confirmed that only approximately half of the depressed patients in the study really benefited or responded to the antidepressant treatment.¹

Full response to antidepressant pharmacotherapy is evident only after several weeks, but considerable improvements may already be visible within the first 2 weeks.² The definition of “early improvement” by Henkel et al is a 50% improvement of the HAM-D₁₇ baseline total score at day 14; remission being defined as a score of ≤7 at discharge. These authors also found that a 20% reduction of the HAM-D₁₇ baseline total score at day 14 predicts response with 75% sensitivity and 59% specificity.³

The several attempts to identify benefits of early improvement in predicting antidepressant response⁴ remain at present controversial, possibly due to several study limitations. First, studies such as that of Mouchabac et al looking at residual symptoms after treated major depressive disorder have found some difficulty in directly linking outcomes in the clinical setting with the HAM-D score. This particular author concluded that poor response and remission are basically due to remaining residual symptoms at the time of response, and the effect of a delay in initiating treatment, which ultimately impacts negatively on early response.⁵ Second, at the response onset, early behavioral effects and the clinical response to antidepressants may involve improvement in some symptoms, but not in others. This reflects only effects that are directly due to the pharmacological properties of the antidepressant and its plasma concentration, but not improvement that is due to the etiology and prognosis of depression.⁶ Third, early antidepressant response in some studies may be gender specific, which may be explained by different auto-endocrinology responses. Fourth, the early response to antidepressants can be attributed to pharmacogenetic susceptibility, which may involve drug metabolism and hence early onset. Last, depressed patients with insomnia tend to have poor clinical outcomes despite the early response of some of their depressive symptoms. Moreover, several studies have shown that clinical response to various antidepressant therapies can be predicted by sleep electroencephalography parameters.

In conclusion, whether early improvement is predictive of antidepressant efficacy remains to be determined. Evaluation of antidepressant efficacy needs more than just evaluation of the pattern and timing of symptom alleviation and outcome, but should include evaluation of detrimental prognostic symptoms such as sleep disturbance or insomnia as well as other residual symptoms, which need an early response for the patient to achieve full remission.

References
It is generally suggested that antidepressant drugs “work” slowly, with Gershon noting the “established belief” that they take 2-6 weeks “to produce their antidepressant activity.” The devil almost certainly lies in the detail, as now detailed. First, the word “work” is capable of multiple definitions. In formal drug trials, “improvement” and “response” status are commonly operationalized as respective reductions in depression severity of at least 20% and 50%, while “remission” is viewed as the absence—or virtual absence—of any symptoms.

While remission—or a euthymic state—is the therapeutic goal, we are increasingly recognizing that full remission (the antidepressant drug has “worked”) is probably only achieved by a minority, with illustrative data from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study quantifying remission rates in the order of 30%, and a responder rate of 47% after up to 3 months of the antidepressant citalopram. Aggregating remitters, responders, and nonresponders in any sample of patients receiving antidepressant drugs therefore contributes to a fairly consistent trajectory pattern, and where, even after 2-3 months, group depression scores are still decreasing, so building the impression that antidepressants require an extended period before they “work.” However, such group trajectories are made up of formally defined “responders” and “nonresponders,” with the nonresponders distorting the quite differing trajectory of improvers and remitters.

If we then limit analysis to prediction of responder status, numerous studies have shown that for such responders, improvement status is achieved in the first week, with evidence of such early improvement also shown for those receiving electroconvulsive therapy.

Do such findings allow us to conclude that early improvement is to be expected of an effective antidepressant? No, possibly, and yes. Caveats to the expectation reflect two principal concerns. First, the majority of the studies examining improvement trajectories with antidepressant drugs have been weighted to patients with nonmelancholic disorders. For those with melancholic and psychotic depression, in the absence of clear data, the impression remains that any improvement may not be evident for several weeks (either as a consequence of the underlying pathogenesis or of the requirement for a certain drug dose to be achieved). Second, placebo responders tend to show evidence of “early onset” improvement, quantified by Quitkin and colleagues as occurring in the first 2 weeks, but generally associated with a subsequent relapse (unless spontaneous remission has been induced or promoted). Turning to the “yes” interpretation, the literature argues against the mythology that antidepressants require weeks or months to work. If a patient is likely to have their depression respond specifically to an antidepressant drug, then some indication of improvement should be evident in the first week or 2—and the improvement trajectory should be maintained. If no such improvement, the clinician might well consider whether the drug dose is insufficient, if augmentation is required, or if another antidepressant drug or other therapeutic paradigm should be contemplated. While there is a minority of individuals who will show a delayed onset effect (ie, improvement occurring after weeks or even months), this appears relatively uncommon and should not dictate clinical practice. As noted previously, if late onset of improvement is a myth, “depressed patients need not necessarily be treated so patiently” by trialing an antidepressant drug for many months.

References
Clinical response and outcome in depression are related to multiple factors. Functional impairment and risk of suicide are two of the major problems at the beginning of treatment. The delayed antidepressant response theory has been dominant in biological and clinical research for more than three decades, despite the initial suggestion of Kuhn and the observation of the immediate inhibitory action of antidepressants on monoamine reuptake.

What is the definition of early improvement? A great number of methodological problems and limitations in the published papers on this topic are relevant: rating scales, frequency of assessments, statistical approaches... Most of the findings come from post-hoc analyses and meta-analyses of trials not specifically designed to detect the early onset of antidepressant action.1

Pooled analysis and systematic reviews or meta-analytic approaches give us a different perspective on the problem, and a positive answer to the controversial question. Forty-seven studies evaluating antidepressant drugs with established efficacy, performing weekly or biweekly evaluations, and presenting the time course of improvement, were included in a meta-analysis: 60% and 61% of the improvement that occurred on active medication or placebo, respectively, took place during the first 2 weeks of treatment. The results suggest that many patients demonstrate a true antidepressant response during the first or the second week of pharmacological treatment.2

Another systematic review and meta-analysis of selective serotonin reuptake inhibitors (SSRIs) identified 50 randomized placebo-controlled trials of these drugs in the short-term treatment of unipolar depression in adults. The analysis supports the hypothesis that SSRIs begin to have observable beneficial effects during the first week of treatment. The effect was seen on the primary outcome of differences in depressive symptom rating scale scores and on the secondary outcome of achieving a 50% reduction in the score.3

A recent review using the Medline database (1966-2007) concluded that a certain group of experimental treatments can produce antidepressant response in a shorter period of time. The authors of the paper considered that a faster and sustained antidepressant response may prevent the neurobiological and psychosocial effects secondary to a recurrent or unremitting depressive episode, and could be a “new paradigm” in antidepressant treatment research.4

The Quitkin-Katz controversy5,6 has a recent chapter, with a post-hoc analysis of a placebo-controlled, randomized, double-blind study of patients with major depressive disorder treated for 8 weeks and then for another 6 months with duloxetine or escitalopram. Improvement at 2 weeks on the 17-item Hamilton Rating Scale for Depression (HAM-D17) significantly predicted remission. Early symptom changes were specific to treatment, with early response for the core depression factors of anxiety and motor activity for duloxetine, and anxiety for escitalopram. In conclusion, lack of early response on depression symptom subscales was highly predictive of a lack of sustained remission. The initial study by Katz et al6 did not include a placebo control group.

Overall, the findings of clinical studies and clinical experience have also confirmed the positive role of early response in predicting clinical outcome. Unfortunately, the published studies have not sufficiently assessed the behavioral changes that might accompany the early drug-induced changes in the monoamine systems. The real problem is how to relate early response to total response and to sustained remission; ie, depression as a chronic or long-term disease. Future research with findings from neuroimaging or pharmacogenetic studies in early response and remission is crucial to improve the outcome of affective patients and to give us a more appropriate answer.

References
Prediction of treatment response at an early stage may have many implications for patients and clinicians. Avoiding unnecessary exposure to ineffective drugs and lessening the negative consequences of depression are two of these. The question of the predictive value of early improvement or antidepressant response goes beyond an old discussion: the timing of the onset of antidepressant response. Three to four weeks’ delay was suggested as a common pattern for antidepressants in the early decades following their introduction. However, there are growing data to suggest early improvement—even as early as 1-2 weeks.1-3

There are two phenomena that have blurred our vision in this field: the placebo effect and the probability of spontaneous remission due to the episodic course of major depression. Differentiation of placebo effect from “true” drug response is the crucial discussion in this controversial issue.

About one third of major depressive patients respond to placebo in drug trials. It is not possible to ignore this nonspecific effect for an active drug. It was suggested that the placebo effect was characterized by early onset of response and a fluctuating pattern, while true drug effect was characterized by a 2-week delay in onset and persistence of improvement, once achieved.4 Delayed persistent improvement was reported to occur about three times more commonly on drug than placebo in this study. The existence of delayed response and delayed persistent improvement has also been shown in another study.5

One method to validate “true” drug effect is to investigate the relationship between early and delayed response and long-term relapse, and several reports have provided some evidence for a delayed response of antidepressants as the “true” drug initial response pattern.6 On the other hand, several investigators have provided considerable data for earlier “true” drug effect,7,8 and moreover, a possible predictive value of it for the treatment outcome.2,3

The main methodologies used to handle this controversial issue are open or randomized controlled trials using comparison groups. In recent times, advanced statistical approaches have been used for better evaluation, such as sensitivity, specificity, predictive values, area under the curve, and survival analysis. Two recent studies with these specific approaches shed light on the area. One of them analyzed data from a naturalistic study on a large sample of inpatients with major depression.1 Results supported early improvement in the first 2 weeks as predictor of later response and remission with high sensitivity in hospitalized patients. The second study2 was a meta-analysis carried out with 6562 patients. The authors concluded that early improvement with antidepressant medication can predict subsequent outcome with high sensitivity. Also, they stressed that there were high negative predictive values and little chance of stable response or remission in the absence of improvement within 2 weeks, and suggested that lack of improvement during the first 2 weeks of therapy might be considered as an indicator regarding earlier changes than conventionally thought.

A closer look at the literature indicates the heterogeneity of both “early/placebo response” and “delayed/true drug response.” Probably both include each other. There could be placebo responders among delayed responders and true drug responders among early responders. We cannot say that all questions are answered and all controversies clarified yet. We need to respect every single study and finding in the literature. Some controversies may be explained with different methodologies and different study populations. On the other hand, it is not possible to handle the issue without considering classification systems, possible subgroups in the category of major depression, differential responses for subgroups, and the heterogeneity of individual responses to antidepressants. Studies designed to consider these issues and to target more representative populations in daily clinical practice may improve our knowledge in this crucial question.

References
This question will address the issue of the importance of feeling beneficial effects early in the treatment course for depression, the symptoms that through their improvement lead patients into remission, and the prediction of a response to treatment.

Patients with depression usually present to the doctor quite some time after they have begun to be depressed. There are different reasons for this delay in presentation and thus treatment. They may not think that they have an illness. Besides this, they may be so depressed that they do not have the motivation to seek medical treatment. On the other hand, they may be so pessimistic that they think they will not recover from the depressed mood. Quite often, they only come to the doctor when their symptoms are so severe that they have become very distressed or suicidal, or the significant people around them are also feeling distressed. Therefore, it is important that treatment should aim to relieve their symptoms and the distress caused within a short period of time.

There are claims that certain antidepressant medications have a faster onset of action than others. However, the evidence is that all the commonly-used antidepressant medications take time to work, usually between 2 to 3 weeks. It is known that time is needed for the drug to reach a steady state in the blood. The serum level also has to be maintained so that changes in the neural circuitry beyond the monoamine receptors (eg, production of brain-derived neurotrophic factor, regeneration of neuronal networks) can occur, ultimately leading to elevation of the depressed mood. Unfortunately, side effects of the drugs will come up before the onset of the antidepressant action, making the patient more miserable and distressed.

Because of this time lag, the patient may lose confidence in the treatment and even take it as a confirmation of their thoughts of hopelessness. Compliance with treatment, which is crucial, will be affected. Nevertheless, if some of the symptoms such as insomnia and agitation can be alleviated at the early phase of treatment, it certainly helps the patient to feel better and to motivate them for further treatment. The direction of further research in the development of antidepressant drugs should be in really achieving earlier onset of mood-elevating action. The future should probably include action beyond the monoamine receptor level or involve a mechanism of action on pathways other than those of the monoamines that we know presently.

Apart from drug treatment, certain psychosocial measures should also be implemented to help the patient to get better sooner. The depressed patient should be encouraged to engage in activities that they can cope with to build up their confidence and self-image. The level of activities can be increased gradually as the mood improves, in order to give the patient more positive experience. They should also undertake regular exercise, as there is evidence that exercise can stimulate the nerves in pathways related to mood regulation. All these measures will help the patient to move into remission sooner.
11. R. M. Zaratiegui, Argentina

The present guidelines advise waiting between 4 to 6 weeks before changing or adapting treatment with antidepressants when there is not at least a partial response. We, as physicians, have got used to warning patients that they will have to wait several weeks to experience a significant improvement. Following research performed at Columbia University, it was considered for a long time that responses prior to a 3-week period of treatment were characteristic of the placebo effect and were not sustained over time (delayed-onset hypothesis). However, there have also been data that show that the antidepressant effect starts before this. The proportion of patients with a 50% drop in the score on a rating scale (usually Hamilton Rating Scale for Depression or the Montgomery–Åsberg Depression Rating Scale) is not the most suitable indicator of the beginning of antidepressant action. In general, there is agreement on the fact that improvement is already clinically noticeable with a 20%-25% drop.

In the last few years, four meta-analyses encompassing trials of several antidepressants versus placebo in more than 5000 patients have shown that active drugs have a higher percent-age of responders even from the first week, and the same or a faster sustained response than placebo. Moreover, the major proportion of the difference seems to be during the first 2 weeks and is not due to the impact of the antidepressant’s sedative effect in the rating scale scores.

A helpful way to find out whether early improvement is a predictor of response or remission consists in calculation of its sensitivity, specificity, and predictive value. It was calculated in the most recent meta-analysis that a 20% improvement on the Hamilton Rating Scale for Depression in the second week was a sensitive indicator of a sustained response after the fourth week (81% to 87% sensitivity), both for antidepressants and for placebo, but not with very high specificity (50%). Quite notably, the absence of early improvement predicted lack of response in 90%, which would suggest that the second week should be a decisive moment at which to instigate any change in the treatment.

The contrast with the established notions seems to be due to the fact that the first studies were carried out with tricyclics and monoamine oxidase inhibitors, drugs of slower titration, and they were also statistically underpowered to detect differences in the first weeks. By contrast, in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, about a third of the responses happened after the sixth week. This is a group estimate without comparison with placebo, which does not mention when the improvement started but does remind us that it takes many weeks to be complete. However, in a naturalistic study in 795 inpatients, it was found that a 20% improvement within 2 weeks could predict 88% of the response at the end of the treatment, but with a low negative predictive value.

Being able to earlier predict the effectiveness of an antidepressant implies earlier adjustment of the treatment, lower exposure to an inefficient drug, morbidity reduction, less work-day loss, and lower family burden, as well as a better use of resources.

To conclude, we have reached a moment at which we should reconsider whether the delayed onset hypothesis must lead treatment in all cases. Under strict conditions, as in the efficacy studies, the evidence seems to justify a change or modification of the treatment toward the end of the second week if the patient does not show any improvement. However, we have to take into account that the effectiveness studies, such as STAR*D, remind us that those patients with comorbidities and other everyday practice–related characteristics tend to respond more slowly.

References
An optimal management strategy in depression to achieve good and complete remission must take into consideration the different time phases of treatment of the disease; from acute short-term treatment, to the maintenance of efficacy phase. Conventional antidepressant treatments have not yet succeeded in achieving this optimal management. Thus, exploration of the relationship between time, rhythmicity, and depression was considered a novel approach to optimizing depression therapy. Valdoxan is a melatonergic MT1/MT2 receptor agonist and a 5-HT2C receptor antagonist, and it responds to the temporal aspects of depression on two levels: in its approach to the pathophysiology of the disease, through the restoration of circadian rhythms, and by providing clinical efficacy at all time phases of depression treatment. Clinical studies have tested the antidepressant efficacy of Valdoxan 25-50 mg at the different time phases versus placebo, selective serotonin reuptake inhibitors (fluoxetine, sertraline), and a serotonin noradrenaline reuptake inhibitor (venlafaxine). Valdoxan has shown earlier symptom improvement compared with placebo, venlafaxine 75-150 mg, and sertraline 50-150 mg, with twice the number of responders as venlafaxine and sertraline. Three pivotal studies have evidenced Valdoxan’s efficacy versus placebo after 6 to 8 weeks on all core symptoms of depression, as well as its superiority to venlafaxine (Clinical Global Impression [CGI]), sertraline (Hamilton Rating Scale for Depression [HAM-D] and CGI), and fluoxetine 20-40 mg (HAM-D and CGI), including in severely depressed patients. After 6 to 10 months of treatment, Valdoxan has been shown to maintain its efficacy, with nearly 8 out of 10 patients free of relapse compared with placebo in a specific maintenance study (P<0.0001), and with superior efficacy to venlafaxine or sertraline. Together, these results demonstrate the early symptomatic improvement, the good efficacy rate, and the prevention of relapse with Valdoxan. Valdoxan is thus able to address the different time phases of depression with unique efficacy, thanks to its novel mechanism of action, by restoring the regulation of circadian rhythms, much altered in depression.

Medicographia. 2010;32:171-177 (see French abstract on page 177)
norepinephrine reuptake inhibitors, norepinephrine-dopamine reuptake inhibitors, etc. All of these, however, address depression with varying degrees of side effects and interactions that compromise their use, as well as being characterized by delayed onset of action and incomplete remission.

It was becoming increasingly clear that a new pharmacological approach was needed to optimize antidepressant treatment. Exploration of the relationship between depression, temporality, and rhythmicity offered a novel basis from which to approach optimization of therapy. Temporality and rhythmicity are markedly disturbed in depression, not only in terms of patient perception of time, but also in biological, physiological, and emotional events, which become erratic and desynchronized, in particular in severe depression and bipolar disorders. Positive mood components are flattened and delayed, and the mood fluctuations increase with the severity of depression.1,2 There is compelling evidence that circadian rhythms are disrupted in depressed patients and that circadian factors may cause depression.3 Affective disorders have been related to circadian rhythms for decades. David Kupfer’s group at the University of Pittsburgh put forward the zeitgeber theory of depression in 1988.4 This approach is being increasingly revisited today. The recent observation of a positive correlation between sleep phase delay and depressive symptom severity has confirmed the relationship between circadian disturbances and depressive disorder in nonseasonal depression.5,6 These recent and historical findings support the hypothesis that circadian abnormalities are a core component of depression. Thus, resynchronizing rhythms via pathways involving the circadian clock and thus normalizing biological homeostasis promises to provide acute and sustained symptom relief, and prevent relapse over the long term. Valdoxan (agomelatine), the first melatonergic antidepressant, acts by regulating circadian rhythms, and its efficacy has been demonstrated versus both placebo7-9 and conventional antidepressants representing the monoamine hypothesis.10-12

![Figure 1. Receptor profiles of antidepressant drugs.](image)

Compared with other available antidepressants, Valdoxan has a novel pharmacological profile: it is the only antidepressant with an affinity for melatonergic receptors. Binding studies indicate that Valdoxan has negligible affinity for α- or β-adrenergic, histaminergic, cholinergic, dopaminergic, or GABAergic (gamma-aminobutyric acid) receptors, and monoaminergic transporters. This innovative profile also accounts for the product’s efficacy and good tolerability. ACh, acetylcholine; TCA, tricyclic antidepressant; †, agonist; ‡, antagonist; ↓, desensitization; +, reuptake inhibition. Adapted from reference 16: Racagni G, Popoli M. Int Clin Psychopharmacol. In Press.

A mode of action based on the resynchronization of time in depression

Valdoxan, a new pharmacological approach to depression, is an agonist at melatonergic MT1 and MT2 receptors and an antagonist at 5-HT2C receptors.13-15 It has negligible affinity for all other central receptors and transporters (Figure 1).16 It does not influence brain serotonin levels as with SSRIs, SNRIs, or TCAs. This unique receptor profile enables Valdoxan to resynchronize circadian rhythms and show antidepressant efficacy in appropriate adapted validated animal models. The ability to regulate circadian rhythms has been replicated in healthy volunteers, in whom Valdoxan phase-advances such rhythms as body temperature, cortisol, and endogenous melatonin release,17,18 and in depressed patients, in whom it regulates the sleep-wake cycle, advances the time to minimum heart rate, and improves the rest/activity cycle.19,20 Preclinical research has shown that the antidepressant efficacy of Valdoxan involves melatonergic as well as 5-HT2C receptors. Both are key players in circadian regulation and depression. Synergy between the two types of receptors has...
been hypothesized as accounting for Valdoxan’s mode of action. The most recent data21-23 show that Valdoxan decreases stress-induced glutamate release in the prefrontal cortex, upregulates the expression of trophic factors (such as brain-derived neurotrophic factor [BDNF]), also in the prefrontal cortex, and increases the survival of newly formed neurons in rat hippocampus. The fact that these effects are not mimicked by melatonin or 5-HT2C antagonists alone supports the hypothesis of synaptic and intracellular signaling synergy in accounting for Valdoxan’s mode of action.

**Antidepressant efficacy of Valdoxan at all time phases of treatment**

Any successful management strategy in depression must take into account another important temporal dimension of depression and its treatment, namely the successive phases and their specific requirements. Efficacy has to be sustained over the acute phase, which requires an early response, the continuation phase, in which the aim is to prevent relapse, and the maintenance phase, where the object is to prevent the recurrence of further episodes.24 Optimization of the management strategy to achieve efficacy in all three phases can ensure complete and sustained remission.

Valdoxan not only reorganizes circadian biological rhythms in depressed patients; in doing so, it also takes into account the temporal dimension of depression and its treatment, enabling clinicians to meet the phase-specific requirements that hold the key to complete remission.

**Acute-phase efficacy: early improvement**

A major problem in treating depression is the delayed onset of antidepressant action that limits the rate of response in the acute treatment phase. Patients showing symptom improvement after treatment for 2 weeks are most likely to be responders.25,26 In other words, early improvement is a highly sensitive predictor of stable response and symptom remission. Initial assessment at the end of this 2-week period in studies with Valdoxan already shows a separation from placebo in the response to Valdoxan.7,8 But clinical improvement on Valdoxan actually starts earlier, within 1 week, significantly faster than on the comparator, venlafaxine10: Valdoxan 25-50 mg was superior in regulating the sleep-wake cycle, as shown by improvement in the ease of getting to sleep (P<0.007) and sleep quality (P=0.015); this was accompanied by an increased sense of feeling good (P<0.001) and improved daytime alertness (P<0.001). This improvement after the first week is so important that even clinicians felt patients were much better on Valdoxan than on venlafaxine: this was reflected by the response rate on the Clinical Global Impression Improvement (CGI-I) scale, which was double that of patients on venlafaxine (19% versus 9%; P<0.01); the difference in score was 0.39, and the 95% confidence interval (CI) was 0.20-0.58 (P<0.0001). A polysomnography study performed in depressed patients objectively confirmed early regulation of the sleep-wake cycle by Valdoxan, showing reorganization of slow-wave sleep during the night from the first week of treatment (P=0.009).15 In another clinical study, versus sertraline 50-100 mg, Valdoxan 25-50 mg significantly improved the rest/activity cycle after treatment for 1 week (P=0.01). The first evaluation on the Hamilton Rating Scale for Depression (HAM-D), after treatment for 2 weeks, showed twice the number of responders among patients treated with Valdoxan than with sertraline (20% versus 10.9%, P=0.027).2 This result is especially important in light of the recent publication by Cipriani et al, which concluded that of the new-generation antidepressants, sertraline was the best choice when starting treatment for depression.27

**Continuation-phase efficacy after the acute treatment phase**

Valdoxan showed antidepressant efficacy versus placebo after 6-8 weeks on the HAM-D and CGI scales in the overall populations of three pivotal studies.7,9 A key issue in demonstrating antidepressant efficacy is the effect in patients with severe depression. Valdoxan has shown efficacy versus placebo in the severely depressed subpopulation, with a maintenance of this efficacy, regardless of symptom severity at inclusion.28 The aforementioned superiority over venlafaxine and sertraline observed in the initial treatment weeks was confirmed after the end of the acute phase of depression. In the study of Valdoxan versus venlafaxine,10 after treatment for 6 weeks, the differences in CGI-I scores were significantly in favor of Valdoxan (Δ=0.32; 95% CI, 0.06-0.5; P<0.05). In the sertraline study, again after treatment for 6 weeks, total scores on the three evaluation scales also differed significantly in favor of Valdoxan: HAM-D (Δ=1.68; 95% CI, 0.15-3.20; P=0.031), CGI-I (Δ=0.29; 95% CI, 0.04-0.54; P=0.023), and CGI Severity (Δ=0.28; 95% CI, 0.01-0.56; P=0.043) (Figure 2, page 174), thus demonstrating the convergence between clinical assessment and the specific measuring instruments.11,20 A specific study in more severely depressed patients showed the superiority of Valdoxan versus fluoxetine 20-40 mg, with a difference in total HAM-D scores of 1.49 (95% CI, 0.020-2.77; P=0.024) and a trend toward a higher responder rate for Valdoxan (71.7% versus 63.8%; P=0.06).12

A meta-analysis of pooled studies versus comparators showed the significantly superior efficacy of Valdoxan after treatment for 6-8 weeks compared with venlafaxine, sertraline, and fluoxetine, with differences of 1.35 in total HAM-D scores (P<0.001) and 0.25 in CGI-I scores (P<0.001). The percentage of responders on both scales was also significantly superior with Valdoxan than with the monoaminergic antidepressants (HAM-D: 72.6% vs 65.1%; P=0.007, and CGI I: 82.2% vs 73.6%; P<0.001).29

**Sustained efficacy of Valdoxan: the maintenance phase**

Valdoxan offers stable protection in the maintenance phase, as demonstrated in a relapse prevention study in which responders to Valdoxan 25-50 mg were then randomized to
remain on Valdoxan or switch to placebo. After treatment for 6 months, the relapse rate on Valdoxan was 21.7% versus 46.6% on placebo \((P<0.0001)\) \(^{30}\). In other words, eight out of ten patients remain relapse-free on Valdoxan, regardless of depression severity. \(^{30}\) Similar results were observed for patients continuing in the Valdoxan and placebo arms up to 10 months. \(^{31}\) Relapse rates on Valdoxan at both time points were less than half those on placebo. The Valdoxan and placebo survival curves only begin to separate at a late time point, 6 to 10 weeks after the discontinuation of Valdoxan to placebo, confirming the previously described lack of withdrawal effect after abrupt cessation of Valdoxan treatment. \(^{32}\)

Valdoxan shows superior maintenance of efficacy to venlafaxine and sertraline. \(^{33}\) The 6-month extensions of the aforementioned head-to-head studies showed a significant difference in total scores on the CGI-I scale of 0.32 (95% CI, 0.04-0.60; \(P<0.05\)) versus venlafaxine, and a superior percentage of responders on the HAM-D scale than with sertraline (76% vs 63.5%; \(P<0.05\)). Overall, these results demonstrate the superiority of Valdoxan in all phases of depression management versus venlafaxine, sertraline, and fluoxetine \((Figure\ 4)\).

### Patient benefits

Adherence is essential if treatment is to be adequate. Valdoxan meets the requirements for maximizing adherence, with excellent compliance in all phases of treatment thanks to the powerful efficacy and benefits that patients can perceive at the start of treatment, during the continuation phase, and during maintenance of treatment. The key to early symptom improvement lies in a unique property that Valdoxan shares with no other available antidepressant: the ability to regulate the sleep-wake cycle with an early sense of increased wellbeing and improved daytime alertness. Furthermore, improvement is accompanied from the early to the late stages of treatment by mild to moderate side effects similar to placebo, such as headache, nausea, dizziness, somnolence, and back pain. Dizziness is the only side effect that occurs significantly more than on placebo, but it occurs in around 5% of patients. Valdoxan has shown no impact on heart rate or blood pressure in clinical studies. Isolated, reversible, and statistically nonsignificant cases of enzyme elevation have been reported (in 1.1% of patients on Valdoxan versus 0.72% on placebo). Thanks to its unique profile, Valdoxan is devoid of the emergent side effects seen with conventional antidepressants. Indeed, clinical studies have confirmed that it is better tolerated than SSRIs or SNRIs, \(^{7,10,34}\) with less patients withdrawn due to emergent adverse events with Valdoxan (6.5%) than with venlafaxine, sertraline, and fluoxetine (10.9%). \(^{29}\)

Valdoxan is also free of discontinuation symptoms, as shown not only by specific in-study questionnaires, but also in a specific trial versus paroxetine using the Discontinuation Emer-
gent Signs and Symptoms checklist. After 1 week of discon-
tinuing Valdoxan, patients were free from emergent adverse
events, whereas after 1 week of discontinuing paroxetine, pa-
tients experienced significantly more discontinuation symp-
toms than those continuing on paroxetine ($P<0.001$).32

The two key side effects of conventional antidepressants
that seriously compromise long-term treatment adherence are
weight gain and sexual dysfunction. Most conventional anti-
depressants, most noticeably TCAs and mirtazapine, induce
short-term weight gain.35,36 In the long term, SSRIs are asso-
ciated with weight gain.37 A recent epidemiological study spec-
ulated that weight gain may be one of the factors responsible
for the increased risk of diabetes associated with current an-
tidepressant therapy.38 Valdoxan, on the other hand, has no
detectable impact on body weight, as shown by the overall
6-month safety data: the mean change from baseline was
0.23 kg versus 0.24 kg on placebo.33

Sexual dysfunction is a common side effect of antidepres-
sants, and has been cited as one of the most common rea-
sons for premature drug discontinuation.39 Patients treated
with Valdoxan, on the other hand, report few sexual side ef-
effects, and these are similar to those reported on placebo.
Two studies have been conducted to evaluate the effect of
Valdoxan on sexual function. In the first, Valdoxan 50 mg was
found to better preserve sexual function in remitted depressed
patients than venlafaxine 150 mg, both on preorgasm and or-
gasm measures.40 The second study was conducted in healthy
volunteers, as the therapeutic effect of drugs on mood in de-
pressed patients can partially mask concomitant undesir-
able effects on sexual function. The results of this study cor-
raborated those of the first study: Valdoxan (25 or 50 mg)
respected sexual functioning, whereas it was impaired with
paroxetine 20 mg.42 The combination of superior efficacy with
the absence of weight gain and sexual dysfunction with Val-
doxan accounts for the higher level of adherence as assessed
after 6 months: a meta-analysis of studies versus active com-
parators revealed that the proportion of patients completing
the studies was significantly superior with Valdoxan (69.4% versus 61.5%; $P<0.05$).39

Conclusion
Valdoxan addresses the different time phases of depression
with unique efficacy, superior to that of the SSRIs and SNRIs.
Valdoxan offers faster improvement after 1-2 weeks, higher ef-
cicacy after 6-8 weeks, and sustained efficacy after 6 months.
Valdoxan: antidepressant efficacy at all time phases of treatment – Munoz

**References**


**Keywords:** circadian rhythm; unique receptor profile; melatonergic; antidepressant efficacy; superior; Valdoxan (agomelatine)
The principal synchronizer in human beings is light. Like almost all beings that inhabit the Earth, the predominant periodicity in humans is circadian. It is light that realigns rhythms that, in turn, are controlled by oscillators—notably the suprachiasmatic nuclei. It appears that the general reduction in sleeping time of nearly 2 hours nightly, observed since the introduction of electric light sources, has had notable consequences on the body weight and blood sugar levels of poor sleepers and insomniacs. It may also favor depression and aggressiveness. In the event of light deficiency, other synchronizers such as work, mealtimes, or group activities can compensate. To measure rhythms in a research context, the core body temperature can be recorded in continuous mode. The blunting or flattening of circadian body temperature rhythms constitutes the biological marker that remains the most specific physiological trait in depression. In clinical practice, it is more practical to use sleep diaries and an actimeter to measure rhythms, before turning to polygraphic sleep recordings. All these measuring instruments enable an objective view of relatively specific criteria for depression. Mood that is worse in the morning and better in the evening is one of the principal clinical markers for major depression, although it is difficult to determine whether this is the cause or consequence of physiological anomalies.

What are social zeitgebers and social rhythms? What are the consequences if they are disturbed?

Originally, human beings were mammals that were both diurnal and arboreal, which means that their strongest sense was that of sight, their principal synchronizer or zeitgeber was light, and like almost all beings inhabiting Earth, their predominant rhythm was circadian, notably their vigilance/sleep rhythm. Since the invention of electricity, humans have probably lost an average of 2 hours of sleep per night. To be more precise, it is generally considered that 1 lost hour of sleep can be attributed to artificial lighting, and an additional hour to television, the Internet, or other electronic stimuli.

It is, however, difficult to confirm such theories objectively and quantitatively, because clearly no sleep recordings existed before electricity was invented. To gain an idea of the real sleeping time of pre-electricity humans, it would be necessary to record the everyday habits of humans in the rare, inaccessible regions of Africa, New Guinea,
and the Amazon basin, where a few ethnic groups still live without artificial light according to a purely day/night rhythm. This would provide an objective view of the average time we would sleep under so-called “natural” conditions. It would not, however, inform us about natural conditions in temperate regions of the world.2

Nevertheless, in a recent and more precisely-conducted study performed in the general population of North America (USA), subjects tested were reported to have probably lost an average of 21.5 minutes of nightly sleep per decade since 1960.3 If this phenomenon persists, we will reach a total of 107.5 minutes’ less nightly sleep in 2010 than in 1960, or indeed nearly 2 hours less. This is a considerable amount, and no one has a precise idea as to its effects on health, but it would be astonishing if there were none. Indeed, there is nothing to suggest that this downward trend is starting to slow, and who knows what figures might ultimately be reached, because we cannot determine the incompressible, “hard core” duration of sleep.

It is generally considered that the ideal amount of nightly sleep in humans averages around 7 to 8 hours, but with major individual variations. The sleep debt is associated with an increased consumption of alcohol, tobacco, and caffeine. Body mass index is correlated with sleep time, which suggests that chronic sleep deprivation at the continental level in North America may be linked to the obesity epidemic that is invading this region of the world.3

Some authors4 consider that the sleep debt is likely to be associated with a risk of diabetes. Although this suggestion remains controversial, it is generally true that insulin resistance is aggravated as sleeping time diminishes. A reduction in sleeping time may also be correlated with a rise in blood pressure.5 Chronic insomniacs have been shown to have lower levels of education and less favorable career paths than those who sleep well. Finally, it is also known that chronic insomnia favors depression or is even a precursor of that condition, to the point where it is thought by some that 20-year-old insomniacs will become 40-year-old depressives.5

However, it should not be forgotten that by definition, epidemiological studies demonstrate associations of phenomena, but never any causal relationships. In other words, one can say that although more obesity is found in insomniacs, this does not necessarily mean that the former is responsible for the latter. Indeed, it is possible to imagine the inverse situation, whereby those who are obese sleep less well because of their weight (experiencing different types of pain, difficulty in breathing, sweating, etc); one can also imagine that if a person sleeps badly, they may go to the refrigerator and eat what they find there. In this latter case, insomnia is the indirect cause of obesity.

A certain number of other arguments highlight the clear link between emotional control and sleeping time. It suffices to spend a night without sleep to understand the degree to which a simple reduction in sleeping time can cause moodiness, aggressiveness, episodes of crying, explosions of rage, and other emotional reactions. All these symptoms are directly linked to the most archaic parts of our brains, collectively called the limbic zone. Under normal circumstances, these areas are linked to the prefrontal lobe, which is the “adult” and reasonable area responsible for our intelligence. Indeed, many authors think that human beings are above all a “prefrontal animal.”

It was in order to allow the development of the prefrontal lobe that our ancestors experienced a gradual diminution of the supraorbital ridge and disappearance of the receding forehead characteristic of most large apes. This part of our brain, capable of controlling instinctive and affective movements, is probably the anatomical seat of what differentiates humans from other animals. Indeed, it has been shown that experimental conditions of sleep deprivation will “disconnect” the prefrontal lobe from the limbic zone. This disconnection deprives the conscious and reasonable part of our brain of any control over emotions, hence an increase in emotiveness and ultimately in violence and aggressiveness. It is therefore possible to hypothesize from these mechanisms that chronic sleep deprivation favors depression, which would help to explain the increased incidence of this condition at a general epidemiological level.6

However, synchronizers other than light do exist in man, but they are difficult to clarify because of the preponderant importance of light. It is in the totally blind, who by definition are deprived of sight and any light stimulation, that these synchronizers can best be demonstrated. In this population, a higher prevalence of insomnia and depression has been noted. When deprived of sight, humans as social animals call upon donors of social rhythms in order to synchronize themselves with their environment, principally by means of hearing: working or family hours indicated by the alarm clock or time clock, television programs, meals, and group activities at fixed times, or in other words, anything that “requires” an individual to adopt regular rhythms.

It is the time of getting up in the morning that forms the basis for different social rhythms, and the “chronotherapist” should use this when proposing a resynchronization program to a depressive patient.2

SELECTED ABBREVIATIONS AND ACRONYMS

DSM-IV Diagnostic and Statistical Manual of Mental Disorders Fourth Edition

PS paradoxical sleep
How can one measure rhythm disruption in depression?

In terms of fundamental research, the most important chronobiological parameter is the circadian rhythm of body temperature. Depression is probably the best example of a disease that results from circadian malfunction. The now historical data acquired by Beersma demonstrated an “extreme blunting or even flattening of circadian body temperature rhythms in depressives.” Body temperature rhythms drive all other circadian rhythms (blood pressure, heart rate, hormones, receptor sensitivity, mitosis, meiosis, etc). They are governed by the suprachiasmatic nuclei (oscillators) and are correlated with what has become known as “form,” i.e., a combination of levels of vigilance, physical and intellectual performance, and mood.

If we accept that major depression is associated with abnormal functioning of the central oscillators, it becomes easy to understand why it is accompanied by excessive vigilance during the night, because there is no change (or only a slight reduction) in nocturnal temperature, and daytime somnolence. This is particularly flagrant in the event of major depression with “melancholy” (Diagnostic and Statistical Manual of Mental Disorders Fourth Edition; DSM IV), where time-related disturbances are of particular importance. Nevertheless, for technical reasons, it remains difficult to record variations in body temperature in everyday clinical practice.

In the context of clinical practice rather than research, a detailed clinical interview regarding lifestyle, and particularly a sleep diary, will enable the best assessment of rhythm disturbances in depression. This simple self-assessment tool for clinical use provides a clear picture of circadian, weekly (social), and monthly rhythms (the latter of particular value in women). The opportunity for a depressed patient to visualize, and thus become aware of, regular variations in rhythm and mood can thus constitute an important therapeutic tool. A “mental pain” item can also be added to the sleep diary that the subject can complete twice a day, once in the morning when getting up and once at around 6 PM, so as to provide an objective assessment of mood fluctuations over the day. The situation most frequently cited is that of the “melancholic feature” of major depression in DSM IV, where a worsening of pain is regularly found in the morning, and an improvement (or lightening) of mood is observed in the evening. This symptom can be considered as a marker of the severity of what was previously referred to as the endogeneity of depression.

In subjects who work, it is common to observe a worsening of depressive mood at the beginning of the week, when social rhythms have been lost during the weekend and have not yet been retrained by professional constraints (Monday mornings). Finally, in women, a gradual and general worsening of mood between ovulation and the start of menstruation, correlated with a blunting of circadian body temperature rhythms, helps us to understand why cases of attempted and successful suicides are significantly more numerous during the week preceding menstruation. Premenstrual syndrome can then be considered as equivalent to depression, as progesterone is a hormone that is both thermogenic (nocturnal), sedative, and depressogenic.

In clinical practice, it is also possible to use an actimeter, an inexpensive instrument like a wristwatch that can continuously record rhythms of movement and inactivity for periods of up to a month. This easy-to-use device can objectively demonstrate vigilance/sleep rhythms and reveal the degree of slowing of depressed subjects during the day.

Finally, polygraphic sleep recordings can be envisaged in some specific cases of insomnia or depressive hypersomnia. However, this remains a complicated procedure when not performed in a research context. The anomalies observed are almost constant, although not very specific when taken in isolation. They are focused on three main areas:

- **Continuity of sleep**: this is the first disorder to have been noted, with a prolongation of sleep latency, and an increase in the number and duration of nighttime awakenings and waking early in the morning, all of which cause a fragmentation phenomenon that reduces the efficacy of sleep.

- **Diminished delta sleep**: this trait has been found by all authors, even if it does not concern all types of depression. Spectral analysis shows that this loss of delta sleep is of major importance during the initial period of sleeping, but that it also persists throughout the night; there is an abnormal distribution of delta sleep, because it is less well represented during the first sleep episode than during the second episode.

- **Paradoxical sleep (PS)**: classically, there is a reduction in the latency of onset of the first period of paradoxical sleep (<90 minutes), and an increase in the duration of this first episode, often accompanied by increases in the density of rapid eye movements and the percentage of PS compared with total sleep.

The specificity of the reduction in PS latency for depressive sleep can reach 70%, and if several of the aforementioned parameters are combined, it is possible to clearly distinguish depressive from healthy sleep, and the sleep of elderly individuals with depression and pseudo-dementia from that of those with Alzheimer’s disease. The association of latency of the first PS episode and prolongation of the first PS episode is a clear sign of depression, although this parameter is not unanimously recognized; some authors consider it as a simple reflection of the number of daytime naps, as depressed individuals adopt clinophilic behavior like those who take naps under normal physiological conditions.

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**Interview**

**Rhythm and blues: social rhythms in depression—from diagnosis to therapy** – Lemoine

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Diurnal mood rhythms in depression: do they result from weakened circadian function? Are there core or associated symptoms more specifically treated by social rhythm therapy?

This issue could be compared to that of the chicken and the egg: which comes first? Is it an anomaly of circadian temperature rhythms that provokes depression, or does the particular behavior of depressed individuals alter their circadian rhythms? At present, it is impossible to answer this question with certainty. Nevertheless, the polysomnographic anomalies observed, notably at the level of PS and delta sleep, appear to persist during remission, which might suggest that they are more a trait of depressives than an effect (state) of depression. It is then possible to hypothesize that a reduction in circadian rhythms, notably those of body temperature, is crucial to the problem of depression, at least in major, severe, and endogenous (unipolar and bipolar) depression.

What type of alleviation of symptoms can social rhythm therapy provide?

Whether we consider antidepressants, thymoregulators, electroconvulsive therapy, light therapy, or cognitive and behavioral therapies, there is a common, final pathway in the event of a positive response, which is an increase in the amplitude of circadian body temperature rhythms. Partial or total sleep deprivation also produces the same result.

Therapy involving adjustment of rhythms must be considered as supplementary to the therapies referred to above. It is thus necessary to reinforce the circadian rhythms through behavioral measures: getting up earlier in the morning (always at the same time), physical exercise immediately on rising, a long hot shower, a relatively high-protein breakfast, and exposure to brilliant white light at 10,000 lux. In the evening, no intensive physical exercise or excessively stimulating or stressful activities, an evening meal containing slow-release carbohydrates, a warm bath, and low lighting to encourage the release of endogenous melatonin.

When these recommendations regarding healthy rhythms are respected, a rapid improvement can be observed in general wellbeing and a reduction in residual symptoms: morning tiredness, insomnia, morning gloominess. Although there is a dearth of studies in this area, it is possible that rigorous compliance with this chronotherapy may to some extent reduce the risk of recurrence.

References

Keywords: light; synchronizer; circadian; social rhythm; measurement; depression; therapy
Rhythm and blues: social rhythms in depression—from diagnosis to therapy – Lemoine

Le synchroniseur principal chez l’homme est la lumière. Comme pour presque tous les habitants de la Terre, son rythme prédominant est circadien. C’est la lumière qui remet en phase les rythmes eux-mêmes régis par des oscillateurs, notamment les noyaux suprachiasmatiques. Il semble que la réduction générale du temps de sommeil observée depuis l’apparition de l’électricité (près de deux heures) ait des conséquences, notamment sur le poids et la glycémie des courts dormeurs et des insomniacs. Elle pourrait aussi favoriser la dépression et l’agressivité. En cas de carence de lumière, d’autres synchroniseurs, travail, repas, activités groupales…) peuvent la pallier. Pour mesurer les rythmes, on peut, dans un cadre de recherche, recueillir en continu la température centrale. L’émoussement, voire l’aplatissement des rythmes circadiens de température centrale constitue un marqueur biologique et demeure le trait physiologique le plus spécifique de la dépression. Il est plus logique en pratique clinique d’utiliser d’abord des agendas de sommeil et un actimètre pour mesurer les rythmes avant de songer aux enregistrements polygraphiques de sommeil. Tous ces instruments de mesure permettent d’objectiver des critères assez spécifiques de la dépression. L’humour pire le matin et meilleure le soir fait partie des grands marqueurs cliniques, même s’il est difficile de savoir si elle est la cause ou la conséquence des anomalies physiologiques.
VALDOXAN : UNE EFFICACITÉ ANTIDÉPRESSIVE À TOUTES LES ÉTAPES DU TRAITEMENT

Pour obtenir une rémission satisfaisante et totale, une stratégie thérapeutique optimale de la dépression doit prendre en compte les différentes étapes du traitement de la maladie, depuis le traitement d’attaque à court terme jusqu’à la phase d’entretien destinée à assurer le maintien de l’efficacité. Les traitements antidépresseurs classiques ne permettent pas encore cette prise en charge optimale. Il fallait donc une nouvelle approche pour améliorer le traitement antidépresseur, s’intéressant aux relations entre le temps, la rythmicité et la dépression. Cette approche est incarnée par Valdoxan, agoniste des récepteurs MT1/MT2 mélatoninergiques et antagoniste des récepteurs 5-HT2C. Valdoxan répond aux aspects temporels de la dépression sur deux niveaux : en restaurant les rythmes circadiens par son approche physiopathologique de la maladie et en apportant une efficacité clinique à toutes les étapes du traitement antidépresseur. Des études cliniques ont analysé l’efficacité antidépressive de Valdoxan 25-50 mg aux différentes étapes versus placebo, versus inhibiteurs sélectifs de la recapture de la sérotonine (fluoxétine, sertraline), et versus un inhibiteur de la recapture de la sérotonine et de la noradrénaline (venlafaxine). Valdoxan a permis une amélioration plus précoce des symptômes qu’avec le placebo, la venlafaxine 75-150 mg et la sertraline 50-150 mg, avec deux fois plus de répondants que la venlafaxine et la sertraline. Valdoxan a démontré son efficacité versus placebo après 6 à 8 semaines dans trois études pivots sur tous les symptômes majeurs de la dépression. Il a aussi prouvé sa supériorité sur la venlafaxine (Clinical Global Impression [CGI]), sur la sertraline (Hamilton Rating Scale for Depression [HAM-D] et CGI), et sur la fluoxétine 20-40 mg (HAM-D et CGI), même chez des patients sévèrement déprimés. Dans une étude spécifique portant sur le traitement d’entretien (p < 0,0001), Valdoxan reste efficace après 6 à 10 mois de traitement, 8 patients sur 10 n’ayant pas rechuté, par rapport au placebo, avec une efficacité supérieure à celle de la venlafaxine ou de la sertraline. L’ensemble de ces résultats montre la rapidité d’installation de l’action de Valdoxan, son taux d’efficacité élevé et sa capacité à réduire les rechutes. Grâce à son mode d’action innovant et son efficacité à toutes les étapes du traitement de la dépression, Valdoxan rétablit la régulation des rythmes circadiens, profondément perturbés chez les patients déprimés.
How does one measure the early onset of antidepressant response?

by S. H. Kennedy, P. Giacobbe, and S. Rizvi, Canada

There is evidence to show that early symptom improvement and early clinical response are predictive of favorable antidepressant outcome at the end of clinical trials. Early improvement describes a reduction in depression score from baseline of at least 20% after 2 weeks, and early response refers to a 50% reduction at or before 4 weeks. Typically, studies have relied on observer-rated scales such as the Hamilton Rating Scale for Depression or the Montgomery-Åsberg Depression Rating Scale. In a few instances, self-report measures including the Beck Depression Inventory or the Hospital Anxiety and Depression Scale have been used for this purpose. However, these scales have generally not been validated for early use and repeated use over time frames of less than 7 days. Patient variables, including personality dimensions, may also bias frequent repeated measurements. Alternatively, the use of physiological measures, including neuroimaging, quantitative electroencephalography, and eye tracking shows promise in objectively detecting biological changes that precede mood improvement, and may distinguish between subsequent responders and nonresponders to treatment. With advances in communication technology, simple approaches such as daily diaries, text messaging, and interactive voice response systems can be employed to measure early “real-time” changes during treatment.
Defining early improvement and early response

There appears to be some consensus on a clinically meaningful definition of early symptom change. “Early improvement” has been operationalized as meaning a reduction of at least 20% from the baseline severity score occurring within 2 weeks, usually based on the 17-item Hamilton Rating Scale for Depression (HAM-D). Similarly, “early response” is considered to be at least a 50% decrease in the HAM-D score on or before week 4 of treatment, while responders after 4 weeks would be classified as “late responders.” The term “early stable responder” would apply to patients who maintained at least a 50% reduction in symptom scores from 4 weeks to the end of a clinical trial.

These definitions have predictive validity in determining subsequent outcomes to antidepressant treatment. For example, Szegedi and colleagues completed a meta-analysis involving patients from over 40 clinical trials, who received either mirtazapine, a comparator, or placebo, and observed that 90% of all “stable responders” at the end of these trials came from the “early improvement” group, while only 11% of stable responders had not been in the early improvement group. These results support previous findings that improvement status at 2 weeks predicts ultimate response status.

Symptom rating scales: clinician-administered

Early onset of action has primarily been assessed using HAM-D, in some reports, using the 21-item version of HAM-D or the Montgomery-Åsberg Depression Rating Scale (MADRS). These clinician-administered scales have been the gold standard in depression measurement for several decades and as such have been included frequently in the literature to assess early response. Several subscales of HAM-D have been validated and compared in depression trials. These include the Maier subscale, and the 7-item HAM-D (HAM-D7), although only the Maier subscale has been used to assess early onset of action. The Maier subscale comprises 6 items of the HAM-D: mood, guilt, work and activities, retardation, agitation, and psychic anxiety. In a post hoc analysis of a duloxetine and escitalopram trial, results demonstrated that failure to achieve a 20% improvement on the Maier subscale was highly predictive of unsuccessful treatment. Using the same measure as well as the HAM-D, a 20% and 30% improvement with duloxetine treatment was observed at 21 days and 35 days, respectively, for both scales.

The Clinical Global Impression (CGI) scale is another measure that has been used to evaluate timelines of early efficacy, based on a clinician’s overall judgment of severity and improvement. Although this simple measure does not assess specific symptoms, it has been found to correlate highly with depression scale scores. Response on this 7-point scale is often defined as a CGI-Improvement score of 1 or 2. Several trials have used this measure to assess early response, with similar results to those with HAM-D.

Symptom rating scales: self-reported

Patient perspective is an important and often neglected issue in measuring symptom improvement. The scales most often used for this purpose are the Beck Depression Inventory-II (BDI-II), the Hospital Anxiety and Depression Scale (HADS), and the Quick Inventory of Depression Scale (QIDS). For the purpose of assessing early onset of action, clinician rating scales have primarily been employed. BDI-II, a 21-item scale, has been used in several pharmacotherapy trials to assess early improvement; however, it is the main measure utilized for tracking patient symptom progression during cognitive behavior therapy. Several studies have used BDI-II to show early improvement in this context. HADS and QIDS, 14-item and 16-item scales, respectively, have also not been utilized frequently in the literature to assess early response.

Limitations of symptom scale measurement

While behavioral measures are a convenient way to assess early response, there are specific issues related to their utiliza-
tion: whether to use a clinician-rated or a patient-rated scale, the frequency of measurement, as well as the time frame for measurement. Each of these variables may significantly influence the outcome of assessments.

Reports suggest that patient and clinician ratings may not necessarily exhibit high correlations. This demonstrates a discrepancy in the findings, whereby patients tend to rate themselves differently to their clinicians. Several studies suggest that the QIDS self report measure correlates highly with both its clinician-administered version as well as other clinician-rated scales such as HAM-D. However, personality dimensions and communication style can significantly weaken these correlations, as was demonstrated by Mattila-Evenden and colleagues using the Comprehensive Psychopathological Rating Scale. Severity of depression has also been shown to influence concordance between self-report and observer-rated scores. Several lines of research suggest that there is less concordance between clinician and self-report ratings during an acute depressive episode compared with repeat tests after patient improvement, although it has been suggested that the increase in rating agreement after patients improve may be a statistical artifact.

The frequency of visits is also an important variable to consider, as an early event may be missed when visits are too infrequent, while too frequent visits may place unacceptable demands on most patients and result in the selection of a subgroup of patients who do not reflect the general population of depressed patients. There is also evidence to show that increased frequency of visits, particularly early on during the treatment, is associated with a higher rate of placebo response. This represents a complication in assessing early improvement, whereby more than one early time point of assessment could significantly reduce depression scores due to the therapeutic effect of visits.

The majority of scales discussed are validated on a set time frame (eg, the past week). However, issues arise when the frequency of assessment deviates from the time frame defined. HAM-D and MADRS were designed to assess the preceeding 7 days; however, if a study necessitates more frequent visits, particularly early on during the treatment, suggests that improvement in emotional processing may occur with the procedure prior to its clinical antidepressant effects. Changes in the neurobiological substrates of emotional processing before and after antidepressant treatment may be a putative endophenotype for early response, and the measurement of these changes can be an indicator for early antidepressant response. There is consistent evidence that patients with depression exhibit biases in attending to, interpreting, and remembering negative emotional stimuli congruent with their mood state. In addition, there is evidence that antidepressant treatments are associated with acute changes in how people process emotional stimuli, and these effects precede any perceived benefit to mood. The facial expression recognition paradigm involves tasks that are able to tap into emotional processing, and features six basic emotions: happiness, surprise, sadness, fear, anger, and disgust, taken from individual characters in the Pictures of Facial Affect series. Several studies have used this task in healthy volunteers to show increased accuracy in identifying facial expressions of fear and happiness independent of reported mood state. Reductions in amygdala response to facial expressions of fear and increased activity in the fusiform gyrus to presentation of happy faces have also been observed, in some cases after just 7 days of treatment.

Similar effects have also been reported in depressed patients using the same paradigm. Specifically, reports suggest that patients receiving an antidepressant demonstrate enhanced recognition of happy facial expressions, decreased reaction time to respond to positive versus negative self-referent items, as well as facilitated recall for positive items, and this in turn may be a predictor of antidepressant response at 6 weeks. In addition, preliminary evidence using the facial expression recognition paradigm in treatment-resistant depressed patients receiving vagus nerve stimulation, a surgical procedure for depression, suggests that improvement in emotional processing may occur with the procedure prior to its clinical antidepressant effects. These results suggest that antidepressants as a class may share the ability to attenuate the cognitive biases seen in depression before changes are seen in the patient’s mood state, and that early detection of changes in emotional processing paradigms hold promise as a predictor of antidepressant response.

**Physiological measurement of early improvement and response**
Measurement scales such as HAM-D, or MADRS are designed to gauge a wide variety of depressive symptomatology from diverse and distinct symptom clusters. As a result, the scores reflect a composite of multiple symptoms that improve at different rates. Methodologically, it is unclear whether early onset of antidepressant effect should be defined based on composite scores or on changes in individual clusters of symptoms. An alternative approach is to explore early changes in specific biomarkers (endophenotypes).

**Emotional processing**
Changes in the neurobiological substrates of emotional processing before and after antidepressant treatment may be a putative endophenotype for early response, and the measurement of these changes can be an indicator for early antidepressant response. There is consistent evidence that patients with depression exhibit biases in attending to, interpreting, and remembering negative emotional stimuli congruent with their mood state. In addition, there is evidence that antidepressant treatments are associated with acute changes in how people process emotional stimuli, and these effects precede any perceived benefit to mood. The facial expression recognition paradigm involves tasks that are able to tap into emotional processing, and features six basic emotions: happiness, surprise, sadness, fear, anger, and disgust, taken from individual characters in the Pictures of Facial Affect series. Several studies have used this task in healthy volunteers to show increased accuracy in identifying facial expressions of fear and happiness independent of reported mood state. Reductions in amygdala response to facial expressions of fear and increased activity in the fusiform gyrus to presentation of happy faces have also been observed, in some cases after just 7 days of treatment.

**Quantitative electroencephalography**
Quantitative electroencephalography (QEEG) is another potential method to assess early antidepressant response, as it has the ability to digitally measure electrical patterns (brainwaves) at the surface of the scalp reflecting cortical activity. After brainwaves are recorded, they are converted into num-
Selective attentional biases

Another promising indicator for detection of early mood change is selective attention to emotionally-laden stimuli. Selective attention to negatively-valenced information supports and sustains the maladaptive patterns of information processing that are characteristic of depressive states, and recent evidence suggests that attentional biases causally alter emotional reactivity to stress. Recent papers have described and validated a new methodology to noninvasively measure changes in selective attentional biases in patients with MDD. In this method, depressed patients and healthy control subjects are asked to scan images with different thematic content while the pattern of their attentional deployment is continuously monitored by an infrared eye-tracking system mounted on the side of a computer monitor. Results from a report employing this task showed that subjects with MDD spent significantly more time looking at images with dysphoric themes compared with healthy controls, and that differences between the fixation times of the two groups was significantly correlated with the valence ratings. The authors concluded that subjects with MDD selectively attend to mood-congruent material, and that depression appears to influence the elaborative stages of processing when dysphoric images are viewed.

Limitations of physiological measurement

Promising methodologies to detect early changes in the processes that putatively contribute to an individual’s mood state include neuroimaging changes in regional activity following the presentation of an emotional facial expression or mood-evoking words, changes in the preference to selectively look at images that are dysphoric versus pleasant, and early changes in measures of regional and global brain activity as measured by QEEG. All of these approaches represent noninvasive means to gauge early changes in brain functioning and the processing of emotional stimuli.

Specifically, there are a number of outstanding questions regarding the role of predicting antidepressant response from early changes in emotional processing. Firstly, the importance of the early changes in affective processing and behavior following acute antidepressant administration to the improvement in subjective and overt mood states is unknown. Antidepressants do not enhance mood in healthy individuals without a history of depression, therefore it is unknown whether the normalization of aberrant neural activity is necessary before clinical effects are seen, or is simply an epiphenomenon. This issue can be addressed through antidepressant trials, in which serial weekly assessments of depressive symptomatology are recorded concurrently with changes in emotional processing paradigms. This experimental design would allow the relationship of these changes to clinical outcome to be determined; namely, whether emotional processing changes invariably precede clinical improvement, what the time lag is between these changes and outcomes on scales, and whether those with a partial or no response to an antidepressant exhibit less change in these emotional processing paradigms.

Secondly, it remains unclear to what extent the immediate effects of antidepressants on the neural substrates of emotional processing interact with the known delayed effects of antidepressants on neurogenesis and neurotrophic factor expression. Studies are needed to assess whether the magnitude of the acute changes in emotional processing seen with antidepressants vary based on illness chronicity, and to what degree the changes relate to neuroimaging findings in depression, such as reduced hippocampal volume. Data to clarify all these issues would help address whether routine screening of these acute changes in emotional processing could be a promising screening paradigm for clinical outcomes.

The challenge for future studies with each of these methodologies is to elucidate their predictive value in a clinical setting. For example, do neuroimaging changes in response to sad facial expressions reliably precede clinically demonstrable changes in mood, and to what extent are residual biases still present in those who achieve antidepressant response? Are changes in selective attentional biases as measured by eye tracking patterns a state or trait marker of mood? Will novel QEEG markers be able to add to this methodology’s superior or temporal resolution and achieve adequate spatial resolution to detect regional changes in brain activity that can predict antidepressant outcomes?

Future directions in measurement

The assessment of the onset of action of antidepressant treatments for MDD has generally been undertaken retrospectively during post-hoc analyses of clinical trials. Since clinical trials are adequately powered to detect a statistically significant effect at the end of the study, typically 4-8 weeks after the initiation of the treatment, standard antidepressant trials may lack adequate statistical power to declare any early changes as significant. A research agenda for future studies assessing the early onset of antidepressant treatments as its primary goal should be based on prospectively designed, controlled, randomized trials, which are adequately powered to detect early onset.
Additionally, in order to measure early response, more frequent data capture is necessary; however, findings of increased placebo response with frequent visits pose a significant complication. Several ways around this issue concern increasing patient involvement in clinical trials. Lenderking and colleagues have been able to show that daily assessment via diary cards in patients receiving open-label fluoxetine had no effect on HAMD-D or MADRS scores obtained in the clinic. In addition, daily diaries were able to detect therapeutic benefits earlier than on weekly assessments.

There is also encouraging evidence that up-to-date technology may aid in capturing more frequent data points. Currently in clinical trials, text message reminders to take the study drug are being implemented. In the same vein, brief questionnaires (eg, Maier, Bech subscale, or HAMD-D) regarding current depressive state could also be delivered via text message. Interactive Voice Response System technology has been in use for over a decade, which allows scales such as HAMD-D to be automated over the phone. This is another relatively unexplored avenue for detecting early response that would enable the gathering of real-time data from patients.

Conclusion Multiple lines of research have begun to challenge the firmly held clinical dictum that the effects of antidepressant treatments are delayed and that treatments require weeks before they exert their effects. A distinction needs to be made between delayed onset and delayed remission with antidepressants. The point has been made in the context of exploring the onset of action of antipsychotic medications, where although there is no debate that full therapeutic benefits take several weeks to realize, this by itself does not imply a delay in the onset of action.

Without future investigations specifically designed to address the issue of time of onset of antidepressants, the time required to achieve improvement runs the risk of being misinterpreted as providing support for a delayed onset of action. Future investigations would benefit from the use of studies that are adequately powered to detect early clinical changes in outcome, refinements in the use of antidepressant measurement scales, and exploration of the relationship between the early neurobiological effects of existing antidepressants and clinical outcomes.

References


**Keywords:** early improvement; early response; major depressive disorder; Hamilton Rating Scale for Depression; quantitative electroencephalography; functional magnetic resonance imaging
In the last decade, EEG tomography techniques such as low-resolution brain electromagnetic tomography (LORETA) have been developed, which enable the intracerebral identification of electrical generators of both disease and drug effects. LORETA combines the high time resolution of the EEG with a source localization method that permits a truly three-dimensional tomography of brain electrical activity.

Since Hans Berger’s early observations of central drug effects visualized with the newly-developed method of the electroencephalogram (EEG), investigators have been trying to utilize the EEG to classify psychopharmacological agents and evaluate their pharmacodynamics at their target organ—the human brain. Initially, trials consisted of eyeball evaluation then in the 1960s and 1970s, computer-assisted quantitative analysis of single lead information (pharmaco-EEG), and from the 1980s onward, of multi-lead analysis and subsequent mapping techniques. It became possible to objectively and quantitatively determine if, how, when, and at which dosage a compound produces an effect on the human central nervous system (CNS). Parallel developments occurred regarding drug effects on event-related potentials and sleep, as well as the search for the neurophysiological correlates of EEG differemnts between psychotropic drugs and placebo in normal subjects, as well as between mental disorder patients and normal controls, it may be possible to choose the optimum drug for a specific patient according to a key-lock principle, whereby the drug should normalize the deviant brain function.

EEG mapping and tomography in drug evaluation

by B. Saletu, P. Anderer, and G. M. Saletu-Zyhlarz, Austria

By quantitative analysis of electroencephalogram (EEG) recordings on the human scalp, in combination with certain statistical procedures (quantitative pharmaco-EEG) and mapping techniques (pharmaco-EEG mapping or topography), it is possible to classify psychotropic substances and to objectively evaluate their bioavailability at the target organ, the human brain. Specifically, one can determine at an early stage of drug development whether a drug is effective in the central nervous system (CNS) compared with placebo, what its clinical efficacy will be like, at which dosage(s) it acts, when it acts, and the equipotency of different galenic formulations. This article describes the pharmaco-EEG maps of representative drugs from different psychotropic drug classes, and the EEG maps of various mental disorders. The relationships between pharmacodynamics and pharmacokinetics, acute and chronic drug effects, alterations in normal subjects and patients, and CNS effects and therapeutic efficacy will be discussed. Imaging of the effects of drugs on regional brain electrical activity in both healthy subjects and patients, using EEG tomography such as low-resolution electromagnetic tomography (LORETA), has been used to identify brain areas predominantly involved in psychopharmacological action. LORETA demonstrates that these psychopharmacological classes affect brain structures differently. By considering EEG differences between psychotropic drugs and placebo in normal subjects, as well as between mental disorder patients and normal controls, it may be possible to choose the optimum drug for a specific patient according to a key-lock principle, whereby the drug should normalize the deviant brain function.
of neuropsychiatric disorders. In the last decade, EEG tomography techniques such as low-resolution brain electromagnetic tomography (LORETA) have been developed, which enable the intracerebral identification of electrical generators of both disease and drug effects.

**EEG mapping of different psychotropic drug classes**

Our own pharmaco-EEG studies in normal subjects demonstrated that a sedative neuroleptic like chlorpromazine 50 mg attenuates total power, increases delta/theta power, and decreases alpha and beta power, with a slowing of all centroids and also of the total centroid (Figure 1). In contrast, the non-sedative neuroleptic haloperidol 3 mg does not change total power, increases delta/theta (predominantly theta), slightly decreases alpha, and increases beta activity, while the centroids remain unchanged.

Sedative antidepressants of the imipramine-amitriptyline type attenuate total power, decrease absolute delta/theta and specifically alpha power, increase relative delta/theta, and decrease relative alpha and to some extent also relative beta power, and slow the total centroid. This is in part contrast to nonsedative antidepressants, since citalopram 20 mg, for instance, also attenuates total power, absolute delta/theta, and alpha power, but increases absolute and relative beta power, slows the delta/theta centroid, and accelerates the alpha and beta centroid, as well as the total centroid.

Daytime tranquilizers such as clobazam 30 mg, decrease total power, absolute and relative delta/theta power, and alpha power, and increase absolute and relative beta power. The

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**SELECTED ABBREVIATIONS AND ACRONYMHS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>CNS</td>
<td>central nervous system</td>
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<tr>
<td>EEG</td>
<td>electroencephalogram</td>
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<td>GAD</td>
<td>generalized anxiety disorder</td>
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<td>HAM-D</td>
<td>Hamilton Rating Scale for Depression</td>
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<tr>
<td>LORETA</td>
<td>low-resolution brain electromagnetic tomography</td>
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<tr>
<td>MANOVA</td>
<td>multivariate analysis of variance</td>
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<td>SAMe</td>
<td>S-adenosyl-L-methionine</td>
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**Figure 1.** Electroencephalogram maps of the differences between nine representative drugs from the major psychopharmacological classes and placebo after acute oral administration (time of pharmacodynamic peak effect, mostly 2nd hour post-drug). Statistical parametric maps depicting intergroup differences in total, absolute, and relative power are shown, as well as the centroids of the delta-theta, alpha, and beta frequency bands (from top to bottom). Bird’s eye view; nose at the top, left ear left, right ear right; white dots indicate electrode positions. Orange, red, and purple colors represent significant increases (P<0.10, P<0.05, and P<0.01, respectively); dark green, light blue, and dark blue indicate significant decreases (P<0.10, P<0.05, and P<0.01, respectively) compared with placebo. In the columns from left to right, different drug-induced changes after single-dose administration of chlorpromazine 50 mg (CPZ50; n=15), haloperidol 3 mg (HAL3; n=20), imipramine 75 mg (IMI75; n=15), citalopram 20 mg (CIT20; n=20), clobazam 30 mg (CLB30; n=15), lorazepam 2 mg (LOR2; n=15), amphetamine 20 mg (AMP20; n=15), metamphetamine 20 mg (MET20; n=20), and pyritinol 600 mg (PYR600; n=12) are topographically displayed. While, for instance, chlorpromazine 50 mg increases absolute delta and theta power and decreases alpha power (CNS sedation), pyritinol 600 mg increases absolute alpha-1 and beta power (vigilance improvement). After reference 27: Saletu B. Pharmacodynamics and EEG. From single-lead pharmaco-EEG to EEG mapping. In: Saletu B, Krijzer F, Ferber G, Anderer P, eds. Electro-physiological Brain Research in Preclinical and Clinical Pharmacology and Related Fields—An Update. Copyright © 2000, Facultas Universitatisverlag.
delta/theta centroid is slowed, as is partly the beta centroid, while the total centroid is accelerated. Nighttime tranquilizers attenuate total power, decrease absolute and relative alpha power, increase absolute and relative beta power, as well as relative delta/theta power, slow the centroid of delta/theta activity and accelerate that of alpha activity, as well as total activity.

Psychostimulants, such as amphetamine 20 mg, attenuate total power, decrease absolute delta/theta, alpha, and beta power, decrease relative delta/theta power, and increase alpha power. The total centroid is accelerated, while after 20 mg amphetamine or 20 mg methylphenidate, differential changes are observed in the centroid of the delta/theta and beta band.

Nootropics and cognition enhancers, such as pyritinol 600 mg, augment total power as well as absolute alpha and beta power, attenuate relative delta/theta power and augment relative alpha power, accelerate the centroid of delta/theta activity and slow the centroid of alpha activity, while the total centroid is accelerated. This is consistent with a vigilance-promoting action on the brain.

**EEG mapping of different psychiatric disorders**

Utilizing standardized recording and analyzing procedures, we found that drug-free schizophrenics demonstrated a decrease in alpha activity, an increase in beta activity, and an acceleration of the beta centroid compared with controls, which suggests a state of hyperarousal in schizophrenia. While schizophrenic patients with predominantly negative symptomatology showed bi-temporal and frontal augmentation of delta/theta, patients with positive symptomatology exhibited an attenuation in these measures (Figure 2). The increase in slow activity suggests an organic factor in the pathogenesis of the negative syndrome. Major depression in the menopause was characterized by a decrease in absolute power in all frequency bands, a tendency toward an augmentation of relative delta/theta and beta and a decrease in alpha activity, as well as by a slowing of the delta/theta centroid and an acceleration of the alpha and beta centroid, reflecting a decrease in vigilance. Generalized anxiety disorder (GAD) patients with nonorganic insomnia showed increased total, absolute delta/theta, and alpha power, as well as relative alpha power, and decreased relative beta power, neurophysiologically reflecting hypervigilance. This pattern is similar to that of another anxiety disor-
der, agoraphobia, with and without panic disorder, which, however, in contrast to GAD, also exhibited augmented beta activity and accelerated delta/theta and alpha centroids. Obsessive-compulsive disorder showed a different pattern of activity, characterized by an attenuation of total and absolute delta/theta and beta power, a decrease in relative delta/theta, and an increase in relative alpha activity, as well as a slowing of the delta/theta centroid. Thus, different anxiety disorders show different electrophysiological patterns.

Demented patients, of both the vascular (multi-infarct dementia) and the degenerative (senile dementia/Alzheimer’s type) subtypes, exhibited a massive augmentation of absolute delta/theta power, an increase in relative delta/theta, a decrease in alpha and beta power, as well as an acceleration of the delta/theta and a slowing of the alpha and beta centroids. Thus, both subtypes of dementia show a vigilance decrement, with differences between them lying in the asymmetry indices and in differences between minimum and maximum power. By vigilance, one understands (since Head) the availability and grade of organization of human adaptive behavior, which is in turn dependent on the dynamic state of the neuronal network. The latter can be measured objectively and quantitatively by computerized EEG analysis. Utilizing neuronal network statistics on absolute delta/theta power findings, we correctly classified 90% of demented patients. Alcohol-dependent patients predominantly showed an increase in absolute and relative beta power and a decrease in alpha and delta/theta power, with an additional slowing of delta/theta and acceleration of the beta centroid.

For the classification of an individual psychiatric patient, one may obtain routine EEG maps of 36 EEG variables, and visualize the differences between the measures of the patient and those of a normal control group by plotting them in terms of the number of standard deviations from the norm (z-scores). An increase in delta/theta power, a decrease in alpha and beta power, and a slowing of the total centroid, for instance, suggest dementia. The ideal drug for such a patient would be the one inducing EEG changes opposite to those caused by the disease, and has to be chosen from one of the aforementioned psychotropic drug classes (key-lock principle).

EEG tomography (LORETA) identifies target regions of drugs and diseases

One of the shortcomings of EEG mapping is that scalp distributions of EEG power cannot be interpreted directly in terms of brain electrical generators. This problem has been over-

![Image of EEG tomography](image)

**Figure 3.** Differences between representative drugs from the four main psychopharmacological classes and placebo in electroencephalogram low-resolution brain electromagnetic tomography (EEG LORETA) power projected to the inflated cortical surface of 20 normal volunteers. Viewed from the top and front. Structural anatomy is shown in gray scale. Red colors indicate increases, blue colors decreases in cerebral cortical activity compared with placebo (P<0.05). Acute oral drug administration of the neuroleptic haloperidol 3 mg, the antidepressant citalopram 20 mg, the tranquilizer lorazepam 2 mg, and the psychostimulant methylphenidate 20 mg induces different regional effects on electrophysiological brain function at the time of pharmacodynamic peak (hours 4, 6, 6, and 4, respectively) in the 7 frequency bands shown. After reference 30: Saletu B, Anderer P, Saletu-Zyhlarz GM. Clin EEG Neurosci. 2006;37:66-80. Copyright © 2006, EEG and Clinical Neuroscience Society (ECNS).
come by LORETA, which computes a unique three-dimensional electrical source distribution by assuming that the smoothest of all possible inverse solutions is the most plausible. This model assumes that neighboring neurons are simultaneously and synchronously active. In a new implementation, an additional neuroanatomical constraint restricts the solution space to cortical gray matter and the hippocampus, as determined in the digitized Probability Atlas (Brain Imaging Center, Montreal Neurologic Institute) based on the Talairach human brain atlas. Thus, LORETA combines the high time resolution of the EEG with a source localization method that permits a truly three-dimensional tomography of brain electrical activity.

Our own LORETA studies demonstrated that representative drugs of the four main psychopharmacological classes such as haloperidol (neuroleptics), citalopram (antidepressants), lorazepam (tranquillizers), and methylphenidate (psychostimulants), affect brain structures differently. Figure 3 shows EEG-LORETA findings after citalopram 20 mg compared with placebo in normal subjects, as well as changes in untreated depressed patients compared with controls. Depressed patients show a significantly decreased LORETA power in the theta and alpha-1 frequency band, and to a smaller extent, regionally decreased delta, beta-1 and beta-2 LORETA power. These findings reflect a deterioration of vigilance, which is the opposite of the vigilance increase induced by citalopram, characterized by an increase in beta-3, beta-2, beta-1, alpha-2 and— to some extent—delta LORETA power. During pretreatment, a negative correlation between LORETA theta power and the Hamilton Rating Scale for Depression (HAM-D) score was observed in the bilateral orbital cortex, the bilateral rostral anterior cingulate cortex, and the right insula cortex; there was a negative correlation between alpha-1 power and the HAM-D score in the right prefrontal cortex. These regions are identical to those Davidson et al described as being involved in affectivity and mood disorders. Pizzagalli et al reported that depressed patients with a higher theta current source density in the rostral anterior cingulate had a better outcome after 4 to 6 months’ nortriptyline treatment than those without this abnormality. The higher theta activity was interpreted as a cingulate hyperactivity, which was described as being reduced after fluoxetine, along with an increase in regional cerebral blood flow in BA, F9, and F46 and in the posterior cingulate gyrus (BA 31). Investigating P300 LORETA changes after S-adenosyl-L-methionine (SAME) administration compared with placebo in elderly normal subjects, we found the same type of changes in identical regions.

Figure 4. Surface-rendered low-resolution brain electromagnetic tomography (LORETA) images on differences between menopausal syndrome patients with depression (n=60) and normal controls (n=29) (upper part) compared with LORETA images on differences between citalopram 20 mg and placebo (6 hours—pre; vigilance-controlled electroencephalogram with eyes closed) in normal subjects (n=20) (lower part).

Images are based on voxel-by-voxel t-values on differences between patients and controls and between drug-induced and placebo-induced changes in the delta, theta, alpha-1, alpha-2, beta-1, beta-2, and beta-3 frequency bands projected to the left and right lateral and the medial cortical surface. Structural anatomy is shown in gray scale (A, anterior; P, posterior; S, superior; I, inferior). Red colors indicate increases and blue colors indicate decreases, as compared with controls/placebo. While untreated depressed patients as compared with normal controls show decreases in LORETA power, specifically in the theta and alpha-1 range (vigilance decrement), citalopram 20 mg as compared with placebo induces an increase in LORETA power, predominantly in the alpha-2, beta-2, and beta-3 bands (vigilance increase).

Time-efficacy relationships in drug evaluation

The time course of the cerebral bioavailability of a psychotropic drug at its target organ—the human brain—can be demonstrated by changes in various EEG variables over time (Figure 5) or on the basis of multivariate statistics utilizing mapping of multivariate analysis of variance (MANOVA) and subsequent Hotelling’s $T^2$ tests. In phase I studies, one has the possibility of objectively and quantitatively evaluating the onset, maximum, and end of the central effect of a drug. These pharmacodynamic changes can be related to pharmacokinetic data (see later), but in patients, the evaluation of single-dose effects may provide valuable insight into the prognostic aspects of a planned treatment (e.g., beta decrease in schizophrenics, delta decrease in dementia patients).

Dose-efficacy relationships in drug evaluation

Dose-efficacy relationships can also be determined based on changes in various EEG variables (Figure 5) and multivariate techniques such as MANOVA with subsequent Hotelling’s $T^2$ tests and mapping techniques. By such means, one can gain insight into the minimal centrally-effective dose in humans, which is important for subsequent open or double-blind placebo-controlled trials, in order to avoid complicated and frustrating investigations in patients. One may also obtain information on changes in CNS effects from certain dosage points onward; for instance, the switch from CNS-activating to CNS-inhibitory effects with benzamides or the changes from a daytime to a nighttime tranquilizer profile with benzodiazepines.

Figure 5. Differences between three doses of ABIO-08/01 and placebo regarding acute, subacute, and superimposed effects on regional electrophysiological brain function analyzed by low-resolution brain electromagnetic tomography (LORETA) in 16 healthy subjects during the eyes-open condition.

Surface-rendered regional electroencephalogram-LORETA differences in seven frequency bands are shown from the top to the bottom. Lateral and medial views from the left and right hemisphere as well as from the bottom are demonstrated from the left to the right. Images depicting statistical parametric maps (SPM) are based on voxel-by-voxel $t$-values of differences between changes induced by the drug and placebo. Red colors indicate increases, blue colors decreases as compared with placebo. Structural anatomy is shown in gray scale. In the 1st hour of day 1, ABIO-08/01 10 mg induces pronounced sedative effects characterized by an increase in delta/theta and beta activity, which changes to a decrease in alpha and beta activity in the 6th hour, with similar findings in the 1st and 6th hour after a superimposed dose on day 5. The subacute effect (hour 0, day 5) is mainly characterized by a decrease in alpha-2 and beta source density.

Bioequipotency in drug evaluation

In a similar way to time-efficacy and dose-efficacy relationships, the bioequipotency of an experimental compound can be explored and compared with that of a clinically well-known drug on the market. This is of special importance for determining the dosage to use in later clinical trials of drugs in patients. Without such calculations, the different intensity of the CNS effects of a drug in normal volunteers and patients would pose a great problem for predicting the optimal single and daily dosages for patients on the basis of phase I trials in normal volunteers.

Relationships between pharmacokinetics and pharmacodynamics

When exploring pharmacokinetic/pharmacodynamic relationships, important information may be gained on: (i) penetration of drugs through the blood-brain barrier to the site of the deep compartment receptor; (ii) receptor binding; (iii) “hit-and-run” phenomena; and (iv) active metabolites. This is of particular interest if there is a time lag between plasma peaks and pharmacodynamic peak effects, such as that observed after the administration of citalopram. If one plots blood levels and EEG changes in the usual two-dimensional graphs for kinetic/dynamic comparison, a scatter appears, suggesting a lack of linear correlation. However, if one shows these points in their time sequence, a system appears in the scatter, resulting in a loop-shaped curve (“hysteresis loop”). This indicates that the maximal pharmacodynamic effect of citalopram is not on the rising, but on the descending, slope of the kinetic curve. The larger the area within the loop, the greater the delay between changes in blood levels and CNS activity.

By exploring pharmacokinetic/pharmacodynamic relationships, we can also discover which of the investigated pharmacodynamic variables are the most sensitive for indicating drug effects, and whether human behavior changes with increasing doses. When determining plasma concentrations after temazepam and flunitrazepam in ng/ml temazepam-equivalents by a radio receptor assay, peak plasma levels were observed for both drugs in the 1st hour after administration, with a rapid decline thereafter for temazepam, while flunitrazepam plasma levels decreased only slowly. Regression and correlation analyses between blood levels and EEG or psychometric changes after temazepam demonstrated that beta activity and the centroid of the EEG were positively correlated with plasma levels, while alpha activity as well as the psychometric variables attention, concentration, the alphabetical reaction test score, the Pauli test score, numerical memory, psychomotor activity, complex reaction, reaction time, flicker frequency, and skin conductance level were negatively correlated with plasma levels. Based on the intercept, it can be concluded that EEG beta activity was the most sensitive variable, followed by the EEG centroid and EEG alpha activity. Psychometric variables started to deteriorate from a blood level of approximately 250 ng/ml upward, while below this level, an improvement can be expected. In fact, blood levels higher than 250 ng/ml were seen only after temazepam 40 mg in the 1st to 6th hour, and after 20 mg in the 1st and 2nd hour. Our findings indicate that 20 and 40 mg temazepam exert sedative, sleep-inducing effects, while 10 mg show rather tranquilizing properties, which was confirmed by all-night polysomnographic studies in sleep-disturbed subjects.

Maps on the correlation between plasma levels and EEG changes can also lead to a better understanding of the pharmacodynamic effects of a novel compound, for instance...
neptine—a glutamatergic modulator. The higher the tianeptine plasma level, the more pronounced was both absolute and relative power in the beta frequency bands, mainly over frontotemporal regions (Figure 6). Furthermore, the higher the plasma levels, the faster the centroid and the higher the centroid deviation of the total activity. These findings indicate a more activating property of tianeptine in the higher investigated dosage range.

**Acute versus chronic effect: changes in normal subjects and in patients**

In contrast to the abundant knowledge of acute drug effects on brain activity in normal subjects, there is a lack of data concerning chronic CNS effects. The reason for this lies mainly in the side effects induced by neuroleptics and antidepressants. However, with the advent of a new generation of antidepressants, the possibility arose of studying compounds with a better tolerability over a longer period of time, even in normal subjects.

On studying the central effects of ademetionine in both younger and older normal subjects, we found in young volunteers pharmaco-EEG maps that were reminiscent of antidepressants of the thymoleptic type, both after acute and subacute administration. In elderly subjects, maps of the thymoleptic type were also observed after acute doses, while after 1 week of daily infusion, a marked increase in total power suggested nootropic drug effects. After administration of anxiolytics and nootropics, we found similar acute and chronic profiles, while after neuroleptics, different changes were observed for acute and chronic time frames. We found differences between the CNS changes induced by a particular drug in normal volunteers and patients, which may not only be due to different sedation thresholds, but more importantly to differences in brain function between untreated patients and normal subjects.

**CNS effectiveness and therapeutic efficacy**

The relationship between drug-induced quantitative EEG changes and therapeutic efficacy can be considered from several viewpoints. Some EEG changes are indicative of certain clinical alterations observed in subsequent clinical trials. There are numerous examples of this relationship in the pharmaco-EEG literature. In this instance, the pharmaco-EEG can be seen as a predictive model in human pharmacology, not unlike the models in animal pharmacology. This applies if the drug-induced EEG changes in normal subjects are different from those in patients. Pharmaco-EEG changes are directly linked to behavioral alterations in both normal subjects and patients. In various studies, we demonstrated that EEG alterations reflecting improved vigilance after acute administration of nootropics in normal elderly subjects were similar to those observed in geriatric and organic brain syndrome patients, which in turn were associated with clinical improvement.

**EEG topography and tomography in the diagnosis and therapy of mental disorders—a key-lock principle?**

Looking closely at the differences between nine major mental disorder patients and normal controls in 15 topographically-displayed EEG measures, and the pharmaco-EEG maps of

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Table.

Electroencephalogram differences between insomniac generalized anxiety disorder (GAD) patients and controls in relation to changes after anxiolytic (benzodiazepine) therapy:

- + = significant P<0.05 increase; ++ = significant P<0.01 increase;
- = significant P<0.05 decrease; -- = significant P<0.01 decrease compared with controls/placebo.
representative drugs from the major psychopharmacological classes, one can see that the differences between patients and normal controls are in certain instances opposite to the changes induced by the drugs compared with placebo.49 This fact speaks for a key-lock principle in diagnosis and psychopharmacological treatment of mental disorders. The EEG differences between GAD patients and normal controls,23 for instance, are the opposite of the changes induced by anxiolytic sedatives compared with placebo in both normal subjects and patients (Table, page 197).49,54 This key-lock principle was also found with regard to the aforementioned depression/citalopram study, as well as in schizophrenia/haloperidol (Figure 7),49 dementia/nicergoline,55 and narcolepsy/modafinil investigations.56 Thus, EEG topography and tomography seem to be valuable instruments not only for early drug evaluation,36 but also for both diagnostic and therapeutic purposes.

References

Keywords: EEG mapping; EEG tomography; LORETA; classification; mental disorder; psychotropic drug; key-lock principle; pharmacodynamics, dose efficacy; time efficacy
Il a été montré qu’une amélioration précoce des symptômes et une réponse clinique précoce sont prédictives d’une évolution antidépressive favorable à l’issue des études cliniques. Une amélioration précoce se traduit par une réduction du score initial de la dépression d’au moins 20 % après 2 semaines et une réponse précoce par une réduction de 50 % à ou avant 4 semaines. Les études cliniques s’appuient généralement sur des échelles d’observation comme l’échelle HAMD (Hamilton Rating Scale for Depression) ou l’échelle MADRS (Montgomery-Åsberg Depression Rating Scale). Parfois, des automesures ont été utilisées à cet effet avec les échelles BDI (Beck Depression Inventory) ou HADS (Hospital Anxiety and Depression Scale). Cependant ces échelles n’ont généralement pas été validées pour un usage précoce et répété sur des périodes de moins de 7 jours. La répétition des mesures peut aussi être biaisée par des variables comme la personnalité du patient. Une alternative prometteuse est représentée par l’utilisation de mesures physiologiques comme la neuro-imagerie, l’électroencéphalographie quantitative et le mouvement oculaire qui permettraient de détecter de façon objective les changements précédant l’amélioration de l’humeur et de donc de distinguer les futurs répondeurs des non-répondeurs au traitement. Grâce aux avancées des technologies de communication, l’emploi de moyens simples comme la tenue de journaux quotidiens, les « textos » et les systèmes interactifs de réponse vocale peuvent permettre d’évaluer les modifications précoces « en temps réel » en cours de traitement.
Melancholy in the arts

Based on the exhibition: Mélancolie – Génie et Folie en Occident
C. Régnier, France

The Temptation of Saint Anthony, by Hieronymus Bosch (c.1450-1516).
Oil on panel. Prado, Madrid, Spain. © Bridgeman Art Library.

Art and Psychosis
Séraphine de Senlis (1864-1942)

A self-taught naïve painter prodigy’s tormented ascent to fame
I. Spaak, France

L’Arbre de Vie. Oil on canvas (114x145 cm), 1928.
Musée d’Art et d’Archéologie de Senlis, France.
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Melancholy in the arts

Based on the exhibition:
Mélancolie – Génie et Folie en Occident

by C. Régnier, France

The Greeks introduced melancholy into medicine, philosophy, and various forms of artistic expression. While physicians related this affliction to black bile (the literal meaning of melancholia in Ancient Greek), philosophers saw it as a “human temperament” linked to affectivity, wisdom, spirit, and reasoning. Throughout history, the fabric of this duality has been woven like warp and weft, conflating mental illness and the artistic temperament plumbing the innermost depths of human suffering. Owned or not as a disease, melancholy has forged intimate and complex links between body and soul. As Jean Clair, Curator of the exhibition Mélancolie—Génie et Folie en Occident, puts it: “There is a physiology and a psychology of melancholy, an anatomy and a chemistry of melancholy, a philosophy and a pharmacy of melancholy, a nosology of melancholy… There is a whole theater of melancholy.” The traits and poses of melancholy have long inspired artists in their countless creations—paintings, engravings, drawings, ancient steles, Rodin’s Thinker lost in his dark thoughts. And there is the melancholic symbolism of the human skull, the open compass, the architect’s tools (like those of the Passion), the balance, the sundial, the hourglass, which reckon weight, space, and time. There too is lead, that saturnine metal (and root of saturnism) which accompanies the melancholic ritual; the animal world thronged with underground, nocturnal, and solitary creatures like the mole and owl, the basilisk with its baleful eyes; the green and yellow of the Elizabethan age, then blue and gray, the hues of melancholy.

Melancholy began its long career in Antiquity as a creature of black bile and madness, journeyed through the Middle Ages in aedic garb, and ever protean shed its Renaissance persona as tortured genius to enter the Age of Romanticism as the embodiment of the most legitimate of the poetical tones. This eventful journey was retraced in the exhibition Mélancolie—Génie et Folie en Occident organized by the Réunion des Musées Nationaux and the Staatliche Museen zu Berlin at the Galeries Nationales du Grand Palais, Paris (October 10, 2005-January 16, 2006), and at the Neue Nationalgalerie, Berlin (February 17-May 7, 2006).

Hippocrates and Aristotle: the medical-philosophical debate on melancholy
In the fifth and fourth centuries before Christ, Hippocrates set forth a “medical” definition of melancholy. The 23rd aphorism (Book VI) gives an extensive explication:
“If a fright or despondency lasts for a long time, it is a melancholic affection.” The Hippocratic Corpus established semiological analogies between melancholy, a quick temper, epilepsy, and madness. Incorporated by Greek physicians into the theory of humors, melancholy was explained by an accumulation of black bile in the human body; this excess could lead to madness. Over the centuries, the debate on melancholy was reduced to a discussion on the nature, cause, flow, and the origin of black bile. This pathology or temperament was deemed to stem from an organic disorder.2,3 Aristotle gave melancholy a philosophical dimension. In his Problem XXX, written in the 4th century before Christ, he asked: “Why is it that all those who have become eminent in philosophy or politics or poetry or the arts are clearly melancholics? Sometimes to the point of being taken by diseases that come from the black bile, as in the heroic legends about Hercules?” Black bile was deemed windy and cold, and to generate narcosis, athymia, apoplexy. But through subtle mixing with the three other humors in what the Greeks called “clotting,” and depending on the anatomical region where it was expressed, it could produce exceptional beings of heightened sensitivity. The melancholic man of genius may be a fragile being, but he fights doggedly against the slide into madness as he steers a course between insanity and reason to achieve wisdom.2

Ancient history and mythology abound with celebrated melancholics whose tales bear witness to this centuries-old medical-philosophical confusion: Plato, Socrates, Lysander afflicted by “melancholic genius,” and Hercules or Ajax in the grip of dementia. Ajax the Great inspired many Greek sculptors and playwrights. Known as the “bulwark of Ajax in the grip of dementia. Ajax the Great inspired many Régnier Lysander afflicted by “melancholic genius,” and Hercules or sophical confusion: Plato, Socrates, to this centuries-old medical-philosophical confusion: Plato, Socrates, Lysander afflicted by “melancholic genius,” and Hercules or Ajax in the grip of dementia. Ajax the Great inspired many Greek sculptors and playwrights. Known as the “bulwark of Ajax in the grip of dementia. Ajax the Great inspired many Greek sculptors and playwrights. Known as the “bulwark of Ajax in the grip of dementia. Ajax the Great inspired many Greek sculptors and playwrights. Known as the “bulwark of Ajax in the grip of dementia. Ajax the Great inspired many Greek sculptors and playwrights. Known as the “bulwark of Ajax in the grip of dementia. Ajax the Great inspired many Greek sculptors and playwrights. Known as the “bulwark of Ajax in the grip of dementia. Ajax the Great inspired many Greek sculptors and playwrights. Known as the “bulwark of Ajax in the grip of dementia. Ajax the Great inspired many Greek sculptors and playwrights. Known as the “bulwark of Ajax in the grip of dementia. Ajax the Great inspired many

From medieval acedia to humanist melancholy

In the Middle Ages, the Church drew parallels between melancholy and Adam’s original sin in the Garden of Eden, and thereafter those prone to melancholy were seen as easy prey for the Devil and his hellhounds. This is the theme of acedia, the forerunner of spleen, itself an archaic trope for melancholy, the refusal of others and of the self. Acedia—listlessness, sloth, disregard for one’s position in the world—particularly afflicted cloistered monks and nuns when lured away from the contemplation and love of God by the Devil. The French writer and critic Charles-Augustin Sainte-Beuve (1804-1869) described acedia in his vast opus published between 1840 and 1859 on the Jansenist Port-Royal Abbey: “Acedia is the world-weakness typical of the cloistered life, above all in the desert when the religious figure lives alone: a vague, obscure, tender sadness, the tediousness of afternoons. Gripped by a yearning for the infinite being, we lose ourselves among ineffable desires.”4 Gustave Flaubert (1821-1880) too describes acedia in The Temptation of Saint Anthony: “How I am bored, cried the anchorite. I would go somewhere, but where I know not; I don’t know what I want, I don’t even have the will to want. Yet to think that I’ve spent my whole life thus, and have never even seen the Pyrrhic dance! It’s pitiful! From where in the devil does this idea come to me?”5 The 1490 painting of The Temptation of Saint Anthony by Hieronymus Bosch (c.1450-1516) depicts the old hermit in the Egyptian desert. Diabolical creatures surround him, a naked woman emerges from a nearby pond, he tilted his head forward, evoking melancholy, but above all resistance to temptation. In The Temptation of Saint Anthony by Otto Dix (1891-1969), painted in 1944, the saint begs the Lord for help, as his hand strays towards, but does not quite touch, a scantily clad and provocative young woman who would not be out of place among the prostitutes of 1920s Berlin.6

Closely linked to melancholy, acedia had well-defined variants: the revolt of bad conscience, cowardliness, torpor, despair, verbiage, so many sins demanding penitence. Acedia was
incorporated into the medieval symbolic imagination to the point that it was personified in the stained glass windows of the cathedrals. The only remedies for this scourge were manual work, prayer, orison, spiritual exercises. The Middle Ages merged the philosophical, religious, and medical principles of melancholy, while associating it with a divine ordeal. At the end of the Middles Ages, Arab alchemists attached the black bile produced by spleen to the influence of Saturn, the planet and god symbolized by lead. The first step in the alchemical transmutation, lead was qualified as the “melancholic state of matter.”

Renaissance humanists revived the taste for melancholy, and the medieval concept of acedia faded away, and is not even mentioned in the monumental The Anatomy of Melancholy by Robert Burton (1575-1640). All mystics became “religious melancholics.” In the famous 1514 engraving by Albrecht Dürer (1471-1528), Melencolia I, the symbolism of the melancholic temperament is fully expressed. The principal figure—Melancholy—is an angel, a genius (i.e., the divinity present in every individual). She sits in a dimly lit corner, head rested on left fist, absorbed in thought, eyes turned to the sea, her right hand holding an open compass, a bunch of keys hanging from her belt. In the background is a coastal landscape in light and shade, a rainbow; hard by a cherub (putto) writes, a dog sleeps, and strewn about are a stone polyhedron (now known as Dürer’s solid), a ruler, a pair of pliers, a saw, an hourglass, a beam balance, four nails, a ladder, a 4 by 4 magic square carved in stone (astrologically associated with Jupiter, thereby tempering the melancholic influence of Saturn). Robert Burton confirmed the great semiological value of the engraving: “Albertus Dürer paints melancholy, like a sad woman leaning on her arm with fixed looks, neglected habit, held therefore by some proud, soft, sottish, or half-mad

Melancholy in the arts – Régnier
and yet of a deep reach, excellent apprehension, judicious, wise, and witty.”8 In turn, the surrealists too praised the symbolic richness of Dürer’s engraving.9

The melancholy of nations
From the 16th century, in England, Spain, Italy, and France, melancholy was expressed through the arts by drawing inspiration from national cultural characteristics.

The melancholic essence of the English disposition was initiated under the reign of Elizabeth I (1533-1603) and reached its apogee in the 17th century. The Elizabethan era is characterized by a cultural and artistic blossoming qualified as the “English renaissance.” Its poetry, plays, and music voiced this destructive and artistically fruitful melancholy. The rest of Europe scoffed at these odd ways, calling them the “English malady.”

*Hamlet* by William Shakespeare (1564-1616) was symbolic: the world’s blackness, the dread of the plot, annihilated by despair, guilt, murderous urges, the imagination tortured by baneful spirits. Only Horatio, the man who is not in thrall to his passions, offers Hamlet a neutral vision of the world. A monument of English melancholy, Robert Burton’s *The Anatomy of Melancholy* published in 1621, tackled the existential and religious questions taxing men and women around the world. This 2000-page miscellany is a collection of quotes, a novel, a catalogue of remedies, a cartography of humanist learning. It summarizes the ambiguity of melancholy, which is both a catastrophe and a distinction: the genius is melancholic.8

Meanwhile, in the Spain of Philip II (1527-1598), proud and stimulating melancholy foreshadowed the decline of a great power. In 1575, the Spanish physician Jan Huarte de San Juan (1530-1588) published *The Examination of Men’s Wits*, in which he describes the varying capacities that distinguish men of different nations and the types of writing corresponding to each. This immensely successful work, translated into several European languages, classified wit and temperament by means of Greek science, but also astrology, the climate, and geography. Unsurprisingly, the Spanish character came closest to truth. And why? Because black bile warmed and purified by the sun enabled the melancholic temperament of the Spanish to cast golden light on the spirit, to dissipate stupor, to illuminate hidden truths. As outstanding theolo-
gians, the Spaniards had the advantage—according to Huarte de San Juan—of easier access to existential truths than the French, Italians, or English. The epitome of this redeeming melancholic Spanish temperament is the eponymous hero of Don Quixote by Miguel de Cervantes (1547-1616) who, between fits of madness, perceives truth and gains wisdom.

In the visual arts, Diego Velázquez (1599-1660), in particular, initiated the representation of the Kings of Spain invariably clothed in black to recall this vital melancholy.

The French, proud of their temperate climate, reputed to be fiery or testy, liked to praise their gay and creative melancholy, sired by eloquence and the quest for beauty and sublimity. Michel de Montaigne (1533-1592), who read Huarte de San Juan, admitted that his somber thoughts could scarce resist the charms of civilized society, of French natural beauty. This temperate climate, according to Louis Pascal de la Court in his imaginary dialogue (1616) between an Italian, a Spaniard, a German, and a Frenchman, favored harmonious expression of the four humors. So the Frenchman was naturally drawn to equilibrium and so to balance of the humors, unlike the German tyrannized by his phlegmatic humor, the Spaniard prone to melancholy, or the Italian victim of his fiery humor. In France, one spoke of “sweet melancholy,” the pleasurable daydreaming that grows out of meditative or thoughtful solitude, a sort of controlled and purposeful sad-
ness. In the 16th century, the French published many treatises on passion explaining how reason can restrain or calm the emotions, however they arise. The wish to control the manifestations of melancholy and to allow the soul to sit above the emotions was an expression of the Cartesian spirit oft attributed to the French. The painter Antoine Watteau (1684-1721), deemed highly strung and meditative, embodied this “sweet melancholy” in country scenes where foreground figures stretch languorously and daydream.

But in the mid 18th century, a warning shot rang out for these geniuses of melancholy. The French physician Anne Charles Lorry (1726-1783), better known for his studies on skin ailments than for his research into mental health, published *De Melancholia et Morbis Melancholis* in 1765. He revised the encyclopedia definition of melancholy as an effect of weakness of the soul and bodily organs, and coined the term “nervous melancholy.” This was a dire blow to the theory of melancholy in the arts – Régnier

**Quotes on Melancholy**

1476 "Saturn seems to have impressed the seal of melancholy on me from the beginning.”
   Marsilio Ficino (1433-1499), Italian translator and philosopher. *Letter to Giovanni Cavalcanti*

1599 "I have neither the scholar’s melancholy, which is emulation, nor the musician’s, which is fantastical, nor the courtier’s, which is proud, nor the soldier’s, which is ambitious, nor the lawyer’s, which is politic, nor the lady’s, which is nice, nor the lover’s, which is all these: but it is a melancholy of mine own, compounded of many simples, extracted from many objects, and indeed the sundry’s contemplation of my travels, in which my often rumination wraps me in a most humorous sadness.”
   William Shakespeare (1564-1616), English playwright and poet. *As You Like It (Act IV Scene I)*

1757 “Men are much oftener thrown on their knees by the melancholy than by the agreeable passions.”
   David Hume (1711-1776), Scottish philosopher. *The Natural History of Religion*

1834 “Her grief had been violent at first in its course, as the quoit hurled forth with all the player’s strength, and like the quoit after many oscillations, each feebler than the last, it had slackened into melancholy. Melancholy is made up of a succession of such oscillations, the first touching upon despair, the last on the border between pain and pleasure; in youth, it is the twilight of dawn; in age, the dusk of night.”
   Honoré de Balzac (1799-1850), French writer. *A Woman of Thirty*

1843 “Besides my other numerous circle of acquaintances I have one more intimate confidant—my melancholy. In the midst of my joy, in the midst of my work, she waves to me, calls me to one side, even though physically I stay put. My melancholy is the most faithfui mistress I have known, what wonder, then, that I love her in return.”
   Søren Kierkegaard (1813-1855), Danish philosopher. *Either/Or*

1851-1862 "I do not pretend that joy cannot be allied with beauty, but I do say that joy is one of its most vulgar ornaments; whereas melancholy is, as it were, its illustrious companion.”
   Charles Baudelaire (1821-1867), French poet. *Journaux intimes*

1881 “All changes, even the most longed for, have their melancholy; for what we leave behind us is part of ourselves; we must die to one life before we can enter another.”
   Anatole France (1844-1924), French writer. *The Crime of Sylvestre Bonnard*

1928 “Melancholy is something too painful, it penetrates too deeply, to the very roots of human existence, for us to abandon it to psychiatrists.”
   Romano Guardini (1885-1968), Italian-born German theologian and philosopher of religion. *Vom Sinn der Schwermut*
humors of the Greeks and to the philosophical approach, as it reduced melancholy to a mental disorder. The French school of alienism, whose leading figures were Philippe Pinel (1745-1826) and Jean-Étienne Esquirol (1772-1840), leapt into the breach, seeking to systematize melancholy, called lypemania, and to classify it among nervous disorders and manifestations of madness.11

Romanticism, the apotheosis of melancholy
By associating melancholy with beauty and “the sublime,” the German philosopher Emmanuel Kant (1724-1804) brought this hazy concept into the sphere of philosophy. In so doing, he launched the romantic era of melancholy. In Observations on the Feeling of the Beautiful and Sublime (1764), he wrote: “the melancholic above all has a sense of the sublime (...) He is acutely sensitive to beauty, which he not only expects to charm him, but also to move him and inspire his admiration. The pleasure he takes in being serious is no less intense.” The melancholic feeling is qualified as “sweet and noble,” and “is engendered by the fright felt by a man intent on some great scheme when he considers the obstacles, the dangers to be overcome, the difficult but great victory that he must win over himself.”

Certain physicians of the early 19th century saw in the melancholic a “disease of the sensitive being” and recommended travel as a cure.12 The writer Étienne Pivert de Senancour (1770-1846) wondered: “From where does man draw the most lasting joy of his heart, this exquisite delight of melancholy, this charm full of secrets which makes him live by his pain and still love himself in the feeling of his ruin?” Forerunners of the impressionists, romantic painters like Camille Corot (1796-1875) and Théodore Rousseau (1812-1867) invented a
Séraphine Louis, the self-taught French painter prodigy born into a peasant family in 1864, left the modern art world with a legacy of work of vivid color and beauty. Mystical and prone to visions, she was discovered by the German art collector Wilhelm Uhde, who provided for and encouraged her, elevating her to the pantheon of French naïve artists between the two World Wars. Séraphine’s mental health gradually deteriorated, until in 1932 she was committed to the Clermont insane asylum, where she eventually died.

What a singular destiny that of Séraphine Louis. Born into a needy peasant community in Picardy, France, in 1864, who could have foreseen that life’s path would lead her to the pantheon of French naïve artists between the two World Wars? Mystical, prone to visions, this fey artist praised by the surrealists painted, she said, at the behest of the Virgin Mary. Ever more mysterious enlaced flowers, leaves, and fruits thrived in the heaven bound “garden of paradise” that grew out of the ramblings of her unconscious mind. Provided for and encouraged by Wilhelm Uhde, the German art collector who discovered Picasso and Henri Rousseau, her works exhibited, Séraphine over the years drifted through visions and fancies and on into madness. Committed to a lunatic asylum in 1932, she died there 10 years later, utterly destitute, leaving to the world of art her numinous experience incarnate in paintings of the “Good Lord’s garden.”

“A n extraordinary passion, a sacred fervor, a medieval ardor.” Thus it was that Wilhelm Uhde, the great German art connoisseur, described the still life paintings of his one-time domestic help, Séraphine Louis. Born into a poor family in Arsy, Picardy (France) on September 2, 1864, Séraphine was elevated by Uhde to the pantheon of French naïve artists between the two World Wars. It is thanks to Uhde, one of the first collectors to champion Le Douanier Rousseau, Picasso, and Braque, that every lover of modern art today can marvel at the fruits and flowers rising heavenward painted by his orphaned, unschooled, friendless protégée in a state of exaltation in a sordid room in Senlis (Picardy). Inspired by nature, the fields and woods where she wandered as a child, not 100 kilometers north of Paris, Séraphine’s art has something of the numinous about it. Her painting, she said, was a response to the divine, to orders from the Virgin Mary. Increasingly undermined by delirium and hallucinations, painting alone in her studio, Séraphine began a slow descent into madness. Committed to the Clermont insane asylum in Picardy in February 1932 because of “chronic psychosis,” abandoned by everyone during the German occupation, the victim of hunger and hardship, Séraphine died there a decade later at the age of 78, never again having taken up another paintbrush.

A decisive encounter
Tired of the hustle and bustle of Parisian life, wearied by the brilliant exhibition he had just devoted to Henri Rousseau, in 1912 Wilhelm Uhde rented a small apartment in Senlis as a weekend bolt-hole. Dining one evening at his neighbors’ house,
Uhde spied a small painting of apples in one corner of the living room. Moved by its beauty and craftsmanship, he thought to himself that “Cézanne would have been pleased to see it.”

“Who painted this?” I enquired.

“Séraphine.”

Not knowing who this could be, I said:

“Which Séraphine?”

“Why... your housekeeper. She was thinking of selling it to us, but if you like it we’ll happily withdraw. It’s eight francs.”

The next day, when she arrived at Uhde’s house for the day’s work, Séraphine noticed her picture propped up on a chair. Not in the least surprised, she laughed. “Sir has bought my painting? Does it please him?”

“Greatly. Do you have others?”

Séraphine hurried home to the rue du Puits-Tiphaine, rushed up the squalid stairs to her garret, grabbed a few canvasses and hastened back. Uhde was overjoyed. The paintings were as beautiful as the first. In them he discerned what Kandinsky called the “inner necessity,” an urge arising from Séraphine’s innermost being, guileless, unstilted, plain. Painted with rare freedom, coated with a kind of varnish, Séraphine’s minutely detailed compositions of fruits, flowers, and leaves were redolent of the illuminations of the Middle Ages.

Uhde tried to learn more, but his artistic housekeeper was close-mouthed: her recipes based on Ripolin paints, moss, earth, holy oil, or blood were a secret. So too was her inspiration. All she revealed in her usual plain-speaking way was:

“What can I tell you, Sir? I paint as I pray. There’s no difference, I always say that I do all this for the Virgin Mary. I paint above all at night when the town is asleep. My still lifes are like gifts for the Good Lord and the Holy Mother. Necklaces of pearls and precious stones that I thread so they’ll be pleased with me. So I’ll go to Paradise.”

“Continue Séraphine,” urged Uhde. “What you’re doing is beautiful. Your fruits are so lifelike, so natural that one almost wants to eat them. And yet no, that’s not quite right. Your fruits are like jewels, the first ever to exist in this world, so pulpy, so ripe under a sun that we have never seen.”

“But the sun is God,” Séraphine replied. “These are the fruits of paradise, that’s how I see it.”

“When I set up there,” Uhde later wrote, “Little did I know that in that great stillness a human destiny was being forged. That here the hallowed heart of a servant was driven to rekindle the sublime of the Middle Ages, to create powerful works of art imbued with the Gothic spirit.”

Uhde watched over his protégée, noted her progress every weekend on arrival in Senlis, helped her with money, and marveled at every new painting. Small boards of wood gave way to canvasses, the colors became more refined, the motifs complex. Yet harbingers of mental ills were already appearing in Séraphine’s works: tentacles sprouted from pomegranates and lemons, plants threatened, eyes glowered from foliage.

*Séraphine de Senlis – Art and Psychosis*  
Wilhelm Uhde. Detail of a larger photo showing a group of avant-garde European artists who patronized the Café du Dôme in Paris.  
Photo taken in February 1910 by Will Howard.  
Billy Klüver Collection. Courtesy of Mrs. Julie Martin. All rights reserved.

*Les Cassis*. Oil on canvas (19x24 cm), circa 1918.

Musée d’Art et d’Archéologie de Senlis, France. © Musée d’Art et d’Archéologie de Senlis; Christian Schryve, Compiegne; © ADAGP

*Les Grenades*. Oil on wood (18.5x23 cm), circa 1920.

Musée d’Art et d’Archéologie de Senlis, France. © Musée d’Art et d’Archéologie de Senlis; Christian Schryve, Compiegne; © ADAGP
L’Arbre du paradis.
Oil on canvas (195 x 130 cm), circa 1929.
Centre Pompidou – Musée National d’Art Moderne, en dépôt au Musée d’Art et d’Archéologie de Senlis.
© Collection Centre Pompidou, Dist. RMN/Jacqueline Hyde.
“Let me paint as I wish, Mister Uhde. I know where I must go. There is no doubt.”
“Wherever you go Séraphine will be fine. And I too will go there.”

A bond of friendship and respect was formed between them, without Séraphine ever acknowledging her protector’s open-handedness. Back in Paris, Uhde showed Séraphine’s work to his “most knowledgeable” friends, and they too were “deeply moved.”

“Make no mistake,” wrote Uhde. “What she paints is in appearance but a narrow world of flowers, leaves, and fruits. Yet this is not rustic decorative painting of the sort to be found anywhere, but one of the most fabulous and powerful works in history, which we judge fairly only if we consider the shepherdess of Arsy as the younger sister of the shepherdess of Domrémy (Jeanne d’Arc).”

A life of toil
When Uhde met Séraphine, she was already 48. Not yet old, but stooped, hands raw from scrubbing floors, cleaning windows, wringing clothes, polishing brass, dusting, scouring. A life of labor begun in childhood.

Her mother, Victorine-Adeline Julie Maillard, a domestic on a farm, a drover, oftentimes a woman of sorrow, died 1 year to the day after Séraphine’s birth. “She was distraught,” said Séraphine, with no why or wherefore. Her clockmaker father, Antoine-Frédéric Louis, repaired pocket watches at fairs, roamed the area setting clocks in homes and farms. Taken ill, “because he couldn’t do without wine” according to Séraphine, he died when she was aged 7. Raised thereafter by her older sister Victorine, who labored in the fields to make ends meet, Séraphine attended to a thousand tasks too grueling for a girl of her tender years. On the suggestion of the priest at Arsy, she attended school from the age of 10 and was a gifted but solitary pupil. To friendship with the village girls Séraphine preferred the intimacy of the woods, of walks in the fields, hours whiled away on the banks of ponds and streams, talking to flowers, poring at plants, marveling over nature’s beauties. Delicate pistils, powdery down on butterfly wings, the miracle of seeds and the slow rise of sap, the enchanting colors of a pheasant’s feather, nothing was a mystery for the young shepherdess. The small church at Arsy too cast its spell in the light of the stained-glass windows, in the bouquets of lilies at the feet of the Virgin Mary, in the singing of canticles. Homeless and lovelorn, Séraphine was enraptured.

From the age of 13, Séraphine worked as a domestic in middle-class homes, first in Paris and then Senlis. Drudge, chambermaid, occasional cook, she was tireless, but whimsical. She stood up to her mistresses, changed employer several times, and dreamed of independence while scrubbing floors. Legend has it that she was a servant in a religious school, where behind the classroom door she eavesdropped on art lessons.

In 1881, Séraphine went to work as a domestic help for the Sisters of Charity of Providence in Clermont, where she remained for the next two decades. “I stayed a long while because I was happy there and the work wasn’t strenuous.”
Admitted to services, Séraphine joined the sisters in prayer and meditation, was filled with hymns and songs, the odor of wax, and the smell of incense, the silence. But her quirks and slovenly dress, her bumptiousness worried the Sisters. And in the town too, Séraphine was gaining a reputation for eccentricity, with her skirts and ample black smock, blouse pinned at the neck with a small pearl brooch—her sole extravagance—her fichus, her unprepossessing countenance, her cotton bundle knotted at four corners, talking to herself and reciting prayers as she walked. Whether it was because she was tired of the bickering of the sisters or of the “crimes” she was convinced she had witnessed within the convent walls, Séraphine left in 1902 and resumed work in town as a char.

In a side chapel in Senlis Cathedral, one day in 1905, an angel’s voice called: “Take up drawing Séraphine, paint for the glory of God. It is Mary’s express wish. I will be back with further instructions. Mary herself will appear to you and order paintings.” Enthralled, Séraphine set to work. Armed with tubes of gouache and oil paint, she withdrew to the scullery to draw bouquets and baskets, everywhere and anywhere: on paper, vases, pitchers, bottles, plates, old shelves, even her furniture. A frenzy of activity. Her awkward fingers regained the nimbleness of a young girl’s. She signed her paintings S. Louis and showed them to her employers, most of whom, whether indifferent or heartening, gave her in return a crust of bread or chunk of cheese. A paltry barter perhaps, but one that helped shorten her hours of drudgery.

Séraphine alone

Séraphine signed her canvasses even before applying the first brushstroke. Working for hours at a stretch, heady with the vapors of terebenthine, lacquers, and house paints, she spurred herself on with her own concoction—“energy wine,” a strange brew of brandy and macerated walnuts. Uhde faithfully bought everything she produced.

But on July 31, 1914, the day Jean Jaurès was assassinated in the Café du Croissant in Paris, on the eve of the Great War, Uhde abandoned his apartment and collections, his friends, and Séraphine too, and returned to Germany. Deserted, reduced to begging, Séraphine fell back on her last hope—painting—and survived in wretched conditions during the First World War in a town forsaken by its people. When the bloodshed finally ended and the people of Senlis returned, Séraphine became something of a laughingstock among the townsfolk. She was mocked for her visions, her faith, her dreams of love. The seamstresses of a local dressmaker’s even toyed with the idea of dressing up as the Holy Virgin, with a blue sash and a veil of tulle. Little did Séraphine care: “Ah, if only you knew how beautiful it is when She comes.” At night, her window open over the town’s rooftops, Séraphine

Séraphine in a few dates

September 3, 1864: Birth at Arsy (Picardy, France)
1912: Meeting with Wilhelm Uhde
1914: Wilhelm Uhde’s return to Germany
October 16, 1927: Exhibition of local artists’ work at Senlis Town Hall. Séraphine’s three paintings bought by Wilhelm Uhde.
1929: Exhibition Les peintres du sacré
January 31, 1932: Séraphine admitted to the lunatic asylum in Clermont (Picardy, France)
1942: Exhibition in Paris: Primitives of the 20th Century
December 11, 1942: Death
1945: On the initiative of Wilhelm Uhde, first exhibition devoted entirely to Séraphine’s work, in Paris

Séraphine Louis painted over 200 works. Some of the 70 that have survived are on display at:
- Musée d’Art et d’Archéologie de Senlis
- Musée Maillol, Paris
- Musée d’Art Moderne, Georges Pompidou Center, Paris
painted and sang canticles. Canvasses of all sizes piled up, always with motifs of flowers, feathers, and fruits, thick materials, soft and downy like fur, pearls, mysterious plants. Solitary, touchy, thinner now, Séraphine dismayed the neighbors with her getups and ragged clothes, an old boater repainted with oils, her odd habits and obsessions. Yet a certain Charles Hallo believed in her. A friend of the painter Albert Guillaume, and President of the Society of the Friends of Art in Senlis, he invited her to exhibit work along with other local artists in the function rooms of the City Hall. On October 16, 1927, the day of the preview, as the other artists put up their dull still lifes, pretty-pretty bouquets, boar and deer hunting scenes, Séraphine hung three canvasses whose sensuality eclipsed them all.
Reunited
Wilhelm Uhde, recently returned to France, read of the ex-
hibition in a local paper and set off for Senlis. “The walls were
covered with paintings, watercolors, drawings of humdrum
provincial art. As I glanced at one after another, in a corner
my eyes suddenly alighted on three large canvasses of
startling power: a bouquet of lilacs in a black vase, a cherry
tree, two laden vinestocks, one of black grapes the other of
white. And while I was contemplating Séraphine’s paintings,
all of a sudden I thought I heard the reawakening of the bells,
long since silent.”

Despite the local press’s gibes at the town’s slightly un-
hinged self-taught painter, Uhde bought the three paint-
ings. He couldn’t wait to find Séraphine. Did she still live in her
miserable attic on the rue du Puits-Tiphaine? He knocked.
“Who’s there?” asked the artist, who opened her door to
scarcely anyone.
“It’s me, Monsieur Uhde.”
The door inched open.
“Monsieur is back?” said Séraphine.
Without wasting a moment, she showed him her work.
“Look Monsieur Uhde, here’s the Good Lord’s garden, see
all the flowers that I have grown there.”

But years of solitude and pauperism had transformed Séra-
phine. She seemed to be struggling with a double person-
ality. On the one hand modest—“It’s terribly difficult. I’m old
and a beginner who hardly knows anything”; on the other ,
paranoid and megalomaniac, signing her canvasses “Séra-
phine Louis, second to none.”

Believing herself persecuted by voices, the old woman
worked barricaded in her room, windows and doors fas-
tened by 40 or more padlocks. A small sign at the bottom of
the stairs warned would-be visitors: “Mademoiselle Séraphine
sees no one.” What did she fear? That someone would steal
her formulas, take her mixtures, those cryptic blends of mud
and moss, holy oil and housepaint, blood? Uhde was dou-
bly compassionate. He admired her work, found everything
she asked for—stretcher bars, colors, varnishes—sent from
Paris by express. The canvasses grew in size as the voices
multiplied inside Séraphine’s head. She imagined a fiancé
back from the war. Spendthrift, she dreamt of buying a town
house and hoarded knick-knacks for her future wedding
home. Once humble, Séraphine became arrogant, no longer
wished to hear of other artists frequented by her patron. Her
canvasses changed, she painted kneeling in a state of un-
controllable exaltation. Inner demons haunted her. Spiteful
eyes stared from bouquets, unsettling insects lurked among
the leaves.

Abandoned by one and all
In 1930, reeling from the economic crisis, the art market col-
lapsed. Uhde pared expenses and warned Séraphine that
he could no longer underwrite her. He distanced himself, and
feeling abandoned she fell into decline. On a glacial January
day in 1932, she put away her canvasses, packed her treas-
ures, and dumped the bundles at the door of the Senlis po-
lice station. Threats and shouts. People wished her ill, she
yelled at the gendarmes as they tried in vain to calm her.

“This legendary figure of Senlis,” the local paper reported,
“suffering from mental deficiency, will doubtless be sent to an
old people’s home where good care will be taken of her. For
this poor unfortunate has lost her way and no longer knows
how to behave or to procure even the bare necessities.”

Committed to the Clermont lunatic asylum, Séraphine was
buried alive among the mad, half-starved and ravaged by the
breast cancer that would kill her a decade later. For a while,
a mysterious benefactor paid Séraphine a small stipend in
an attempt to improve her everyday fare. Was this a final
gesture by Wilhelm Uhde?

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ART ET PSYCHOSE - SÉRAPHINE DE SENLIS (1864-1942):
LE CHEMIN D’OMBRES ET DE LUMIÈRE D’UN PEINTRE NAÏF AUTODIDACTE

Quel étrange destin que celui de Séraphine Louis, pauvre paysanne née le 3 septembre 1864 à Arsy dans l’Oise et
érigée au panthéon de l’art naïf français entre les deux guerres. Peintre mystique, sujette à des visions, cette sin-
gulière artiste encensée par les surréalistes disait répondre à la voix d’un ange qui lui transmettait les ordres de la
Vierge Marie. Entrelacs de fleurs, de plumes, de feuilles et de fruits de plus en plus grands, de plus en plus mys-
térieux, son extraordinaire « jardin de Paradis » puise sa force dans les méandres de son inconscient pour s’élever
vers le ciel. Malgré les encouragements, le soutien financier et les expositions que lui organise Wilhelm Uhde, collec-
tionneur allemand et découvreur de Picasso et du Douanier Rousseau, Séraphine finit par succomber à ses hallu-
cinations. Internée à l’asile d’aliénés de Clermont-de-l’Oise, elle y meurt le 11 janvier 1942 à 78 ans dans le plus grand
dénouement. Son œuvre magistrale compte plus de 200 toiles, dont seulement 70 sauvées aujourd’hui des destruc-
tions et de l’oubli.

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new symbolism: they depicted states of the melancholic soul by the representation of nature, which became the central motif of their works. In literature, the great school of modern melancholy is represented by François René de Chateaubriand (1768-1848), whose hero René in his eponymous novella drags his gloomy figure through an “empty world.” With his “rich, prolific and marvelous” imagination, young René is afflicted by a disease of the soul that renders his existence “wretched, barren, and disenchanted.” Generations of French writers adulated and sought to emulate René, to the point that Chateaubriand wrote in his Mémoires d’Outre-tombe (1848-1850) that:

If René did not exist, I would not write it again; if it were possible for me to destroy it, I would destroy it. It spawned a whole family of René poets and René prose-mongers; all we hear nowadays are pitiful and disjointed phrases; the only subject is gales and storms, and unknown ills moaned out to the clouds and to the night. There’s not a top who has just left college who hasn’t dreamt he was the most unfortunate of men (…) In René, I exposed an infirmity of my century. 

Then came Charles Baudelaire (1821-1867), the poet of melancholy, bard of the estheticism of unhappiness, who denounced joy as a vulgar ornament of beauty and made melancholy his illustrious companion.

References


Les Grecs ont introduit la « mélancolie » en médecine, en philosophie et dans les différentes formes d’expression artistique. Si les médecins rapportèrent cette maladie à la bile noire, les philosophes en firent un « tempérament humain » lié à l’affectivité, la sagesse, le génie et le raisonnement. Au cours de l’histoire, ces deux approches de la mélancolie se chevauchèrent en permanence, d’où la difficulté de distinguer la pathologie mentale du tempérament humain » lié à l’affectivité, la sagesse, le génie et le raisonnement. Au cours de l’histoire, ces deux approches de la mélancolie se chevauchèrent en permanence, d’où la difficulté de distinguer la pathologie mentale du tempérament humain » lié à l’affectivité, la sagesse, le génie et le raisonnement. Au cours de l’histoire, ces deux approches de la mélancolie se chevauchèrent en permanence, d’où la difficulté de distinguer la pathologie mentale du tempérament humain » lié à l’affectivité, la sagesse, le génie et le raisonnement. Au cours de l’histoire, ces deux approches de la mélancolie se chevauchèrent en permanence, d’où la difficulté de distinguer la pathologie mentale du tempérament humain » lié à l’affectivité, la sagesse, le génie et le raisonnement. Au cours de l’histoire, ces deux approches de la mélancolie se chevauchèrent en permanence, d’où la difficulté de distinguer la pathologie mentale du tempérament humain » lié à l’affectivité, la sagesse, le génie et le raisonnement. Au cours de l’histoire, ces deux approches de la mélancolie se chevauchèrent en permanence, d’où la difficulté de distinguer la pathologie mentale du tempérament humain » lié à l’affectivité, la sagesse, le génie et le raisonnement. Au cours de l’histoire, ces deux approches de la mélancolie se chevauchèrent en permanence, d’où la difficulté de distinguer la pathologie mentale du tempérament humain » lié à l’affectivité, la sagesse, le génie et le raisonnement. Au cours de l’histoire, ces deux approches de la mélancolie se chevauchèrent en permanence, d’où la difficulté de distinguer la pathologie mentale du tempérament humain. 

Méthodologie et présentation d’œuvres

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